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RESEARCH ARTICLE

A CLINICOPATHOLOGICAL STUDY AND MANAGEMENT OF GASTROINTESTINAL STROMAL TUMOUR (GIST)

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Abstract

Background and aim : Gastrointestinal stromal tumor (GIST) is the most common sarcoma of gastrointestinal tract. GISTs account for approximately 80% of gastrointestinal mesenchymal tumours. The aim of the study is to determine the clinico-pathological features and management of primary gastrointestinal stromal tumors [GIST] and its therapeutic outcome in a Tertiary care Hospital. **Materials and methods**: This is an observational study. 14 patients having GIST were diagnosed and treated over a period of last 7 years in the Department of Surgery at NKP Salve Institute of Medical Sciences , Nagpur. Analysis of the clinical presentation, method of diagnosis, locations of the tumours, surgical treatment, histopathological findings, and postoperative outcomes were done. **Result:** There were 10 males and 4 females with a median age of 55 years. All patients were symptomatic and abdominal pain was the most common symptom. The primary sites of GIST were mostly occur in the stomach and small intestine with rare occurrence in the rectum , colon . 92% of cases were CD 117 Positive. Surgery was considered in all 14 patients, liver was the main site of metastasis . Imatinib improved the rate of survival and post operative recurrence and the metastasis was decreased. **Conclusion:** Abdomen pain is the common presenting symptom. The majority of the cases treated by surgery and the use of adjuvant imatinib had good prognosis .The five year survival rate declines and prognosis becomes poor with increase in the size and mitotic activity.

Keywords:. GIST, Imatinib, Prognosis, Histopathology, immunohistochemistry

INTRODUCTION

GISTs (Gastro Intestinal Stromal Tumors) are a subset of mesenchymal tumors and represent the most common mesenchymal neoplasms of Gastrointestinal tract and account for < 1% of all gastrointestinal neoplasms. Gastrointestinal Stromal tumors are KIT-expressing and KIT (tyrosine kinase receptor - CD117)-signaling driven mesenchymal tumors (1). GISTs include most tumours previously designated as leiomyoma, cellular leiomyoma, leiomyoblastoma and leiomyosarcoma (2). GISTs are believed to originate from a mesenchymal stem cell that differentiates towards an Interstitial Cell of Cajal phenotype . GISTs are characterized with diverse clinical presentations, including acute and chronic gastrointestinal bleeding, abdominal pain, presence of an abdominal mass, anorexia and intestinal obstruction (3). The majority of GISTs arise in the stomach (60%) and small bowel (30%); the remaining 10% in the esophagus and rectum (4). Presently, the defining feature of GIST is the expression of CD117, a marker of KIT activation, which is sensitive although not entirely specific. Surgical resection of the local

disease is the gold standard therapy. Its goal is complete resection of the disease with avoidance of tumor rupture (5). Complete surgical resection is connected with 48-65% five year survival [6] . The advent of Imatinib has markedly altered the clinical approach to GIST. It has proven to be effective in metastatic GIST and is also as a neoadjuvant and adjuvant therapy (7).

MATERIAL AND METHODS

A total of 14 patients with GIST diagnosed at Tertiary Care Hospital over a period of 7 years were studied prospectively and a follow up was made . The laboratory and radiological work- up done. The demographics, clinical presentation , the lab investigations and computed tomography (CT), magnetic resonance imaging (MRI) and endoscopy findings were collected. The immunohistochemical profile was performed using a panel of CD117, CD34, and S100. The main prognostic factors, such as size, mitotic index, rupture, metastatic lymph nodes details were collected and Fletcher's classification (8) was used (Table 1). The type of resection performed was classified as R0 if there was no residual disease or microscopic involvement of surgical resection; R1 when there was residual disease; and R2 when there was macroscopic residual disease. In the evaluation of treatment outcomes, we analyzed overall survival and disease-free survival, survival after introduction of imatinib. Treatment with imatinib was ranked neoadjuvant when performed prior to surgery.

Table 1. Estimated malignancy potential (Fletcher et al.).

Malignancy risk	**Size (cms)**	**Mitotic (50 hmf)**
Very low	<2	<5
Low	2-5	<5
Intermediate	< 5 5-10	6 –10 >5
High	>10 Any size	Any index >10

RESULTS

14 patients underwent surgical intervention for GIST at tertiary care hospital. Mean age was 55 years (range, 35-72 and prevalence was slightly higher in males (71%). Pain in abdomen was a common complaint accompanied with other complaints of either lump in abdomen or generalized weakness. Clinical presentation varied according to the site of GIST.

Table 2: shows clinical features and radiodiagnostic findings of GIST at different sites:

Sites	Clinical features	Radiodiagnostic findings
Stomach	pain in abdomen loss of appetite generalised weakness per abdomen= epigastric rounded, fixed, tender mass	USG- rounded, heteroechoic, well defined, pedunculated, vascular mass with calcification, noted in the body of stomach CT scan- exophytic, cavitatory, moderately enhancing growth communicating with stomach posteriorly, involving left lobe of liver.
Small Bowel	pain in lower abdomen, intermittent, colicky per abdomen= tenderness in hypogastrium	USG- heteroechoic mass arising from the small bowel in the infraumbilical region, 8x5x4 cm, with increased vascularity
Rectum	bleeding per rectum tenesmus	CT - bowel wall thickening involving sigmoid and rectum, 8cm long and 3.9cm thick, likely malignant.
Esophagus	Dysphagia Pain in abdomen	CT- Endophytic growth in lower third of esophagus extending towards the gastroesophageal junction.
Retroperitonium	pain in abdomen, intermittent, dull aching per abdomen= mild tenderness in epigastrium	CT scan- solid tumour measuring 4x3.5x3 cm in the retroperitoneum between the abdominal aorta and IVC, compressing the pancreas

For example, difficulty in defecation and per rectal bleeding for rectal GIST, where as lump in epigastrium for gastric GIST. The majority of tumors were located in the stomach (8 cases, 57.1%). The others were found in the small bowel (3 cases, 21.4%); 2 in the ileum and 1 in the jejunum , Retroperitoneum (1 case, 7.14%), esophagus (one case, 7.14%) and rectum (one case, 7.14%). Tumor size varied between 1 and 30 cm, with a mean diameter of 7 cm. The clinical features and radiodiagnostic findings were shown in Table 2.

Table 3: Shows operative procedures performed for GIST at different sites , histopathology and immunohistochemistry:

Sites	Operative procedures	Histopathology	Immunohistochemistry
Stomach	Total gastrectomies	Increased cellularity, mixed cell type, Tumor necrosis was seen	CD117+ CD34+
Small bowel	Excision of affected jejunal segment with end to end jejuno-jejunal anastomosis Excision of affected ileum segment with end to end anastomosis.	Spindle cells in majority, with epitheloid cells and mixed pattern at places; low mitotic activity	KIT, SMA, Desmin
Rectum	Anterior resection	intramural highly cellular mass composed of spindle cell.	CD117+ CD34+
Retroperitonium	Debulking of the tumour	Hypocellular tumours composed of spindle cells	CD34+, Vimentin
Esophagus	Subtotal esophagectomy with proximal gastrectomy	Mixed spindle and epitheloid cell morphology was found	KIT, SMA

All 14 patients underwent exploratory laparotomy and lesion was primarily dealt with . Total excision of the tumour was possible in all cases except two of which one had GIST located in the lesser curvature of stomach infiltrating into the lesser sac. Other GIST located in retroperitonium extending upto abdominal aorta posteriorly making it nonresectable. Debulking of the tumour was done. R0 resection was performed in 85.7% of the cases, R1 in 7.1% (1 cases) and R2 in 7.1% (one case). Using Fletcher's classification (8), 3 out of 14 cases (21%) were high risk, 3 (21%) intermediate and 8 (57%) low risk tumors. Postoperative period of all patients were uneventful. .In the last 5years of follow up, 11 of these patients did not present with any signs of either disease recurrence or its dissemination. The one with gastric GIST came with recurrence and liver metastasis within 2 years of surgery. He is presently on Imatinib drug therapy . All patients are receiving Imatinib with good compliance.

DISCUSSION

During the last 10 years, since the GIST has been recognized as a well-defined pathological entity with its own characteristics, the surgical management of GISTs has changed. The lack of lymphatic spread of this kind of tumor makes lymphadenectomy unnecessary, so the only oncological criteria is to maintain the integrity of the capsule and to perform an R0 resection. GISTs occur in the entire gastrointestinal (GI) tract and are the most common mesenchymal tumours of the GI tract. A great majority of them occur in the stomach (60% to 70%) and small intestine (25% to 35%), with rare occurrence in the colon and rectum (5%), oesophagus (<2%) and appendix. DeMatteo et al (9) reported a median age of 58, with predominant localization of the tumors in the stomach (39%) followed by small bowel (32%). Ahmed et al (10) reported a mean age of 64.4, with tumors mainly localized in the stomach (52%) and colon (13%). GISTs are characterized with diverse clinical presentations, including acute and chronic GI bleeding, abdominal pain, presence of an intra-abdominal mass, anorexia and intestinal obstruction [3].
The R0 resection rate was higher in our series (85.7%) than in others: DeMatteo et al (9) reported 47%; Ahmed et al (10) 51%. The difference can be explained by the larger number of patients in those series. GISTs can be histologically identified as highly cellular spindle cell or epitheloid mesenchymal tumours and morphology is somewhat site dependent. However, common to all these tumours is expression of KIT (CD 117 antigen), which is a major diagnostic criterion [11].
Tumors designated as GIST stained positively for CD117. The present study, 92.7% tumors morphologically designated as GIST stained positively for CD117. It is usually accepted currently that all GISTs are not CD117 positive and CD117 negative tumors are usually associated with mutation of PDGFRA [12]. In the largest series of 1768 gastric GIST by Miettinen et al [13]., 91% tumors were reported to be CD117 positive. Complete surgical resection is the most important means of cure for GISTs (14). Aggressive surgical resection, achieving complete resection, can lead to prolongation of life and may be a potential cure for patients with GISTs (15). In the evaluation of treatment outcomes, the overall survival and disease-free survival, survival after introduction of imatinib was good.A KIT tyrosine kinase inhibitor, STI-571 (Imatinib) has recently shown promise in the treatment of metastatic GISTs (11)]. It has proven to be effective in metastatic GISTs and is also under investigation as a neoadjuvant and adjuvant therapy (7). 5 year survival following surgical resection varies between 35% to 65% (16).

CONCLUSION

92% of cases were CD 117 Positive. A multidisciplinary approach to this pathology is essential, a fact that affects prognosis and patient survival. Surgical treatment remains the gold standard therapy for resectable GISTs. In the presence of resectable and non metastatic masses, correctly removed by the surgeon, pathological and biological features of the tumor, expressed by Fletcher's classification, remain the most important factors for predicting the prognosis. For high risk or metastatic tumors as for non resectable masses, molecular therapy with the tyrosine kinase inhibitor imatinib mesylate has improved survival.

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