Gastrointestinal Stromal Tumours: Review of 150 Cases from a Single Centre

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Abstract Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract. They constitute a significant percentage ranging from 1–2 % of all the gastrointestinal neoplasms [11]. Knowledge on the molecular biology and behavior of these tumours is still not very clear. The clinicopathological features are variable and surgical resection with chemotherapy is the main modality of treatment. We have retrospectively analyzed the clinicopathological features, treatment and prognosis of 150 patients managed in the Department of Surgery. Retrospective review of the records of 150 patients diagnosed with gastrointestinal stromal tumours and managed during the period January 2006 to December 2011. Clinicopathological features, immunohistochemistry, mitotic index, surgical resection adjuvant chemotherapy and survival analyzed. One hundred and fifty patients diagnosed with GIST and treated were reviewed. Ninety five of them were males (63.3 %). The tumour was most commonly seen during the fourth and fifth decades of life. Abdominal pain (52 %), intestinal bleeding (40 %) and abdominal mass (25 %) were the common clinical symptoms. Sixty percent of the tumours (90/150) were located in the stomach followed by small bowel (20 %) and duodenum (14.6 %). One hundred and thirty-five patients underwent excision of the tumour and five patients had multi organ resection of the adjacent organs like spleen, tail of the pancreas and kidney. Fifteen patients (10 %) received neoadjuvant Imatinib for down staging of the tumour prior to surgery. The tumour

size ranged from 1 to 34 cm. One third of the tumours (42/150) belonged to the high-grade category. KIT protein (CD117) was positive in 90 % (135/150), while CD34 was positive in 50 % (74/150) of tumours. Majority of the patients with high and intermediate-risk category received adjuvant Imatinib (65/77). Seventeen patients (11.3 %) developed recurrence of the tumour on follow-up and rest of the patients had stable disease. Eight of the 15 patients (53 %) who had advanced disease developed recurrence of the disease over 6 months to 1 year. Fifteen patients died on follow-up between 2 and 5 years. Gastrointestinal tumours are the most common non epithelial tumour of the GIT. GISTs are found to show a male preponderance and are common during the fourth and fifth decades. Abdominal pain and intestinal bleeding are the most common clinical presentation. Most of the tumours were located in the stomach. Surgical resection is the best modality of treatment for operable lesions. Tyrosine kinase receptor (KIT) inhibitor like imatinib is used for adjuvant treatment. Regular follow-up with ultra sonogram or computed tomogram helps in diagnosing disease recurrence.

Keyword Gastrointestinal stromal tumours · Surgical resection · Chemotherapy · Prognosis

Introduction

Gastrointestinal stromal tumours are the most common mesenchymal neoplasms of the gastrointestinal tract [1]. The tumours have variable clinical presentation from being asymptomatic to rapidly progressive malignancies. They can occur anywhere throughout the gastrointestinal tract and are seen most commonly in the stomach (60 %) followed by small bowel (30 %). They constitute 2 % of gastric tumours and 14 % of tumours found in the small intestinal tumours [2].

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Gastrointestinal stromal tumours (GIST) originate from the intestinal cells of Cajal, also known as ‘pace makers’ of the gastrointestinal tract. The tumour cells express KIT2 a tyrosine kinase receptor encoded by the oncogene KIT2 [3]. Activating KIT mutations have been found to be of pathogenic importance in most GISTs [3, 4]. Immunohistochemical markers CD117 for the KIT protein has been helpful in distinguishing GIST from other mesenchymal tumours like leiomyoma, leiomyosarcoma and leiomyoblastoma. Majority of patients with GIST benefit from tyrosine kinase inhibitor therapy and treatment improved survival significantly [5].

GISTs have varying malignancy potential. The aim of this review is to understand the clinical presentation, pathological features, treatment and survival of patients with GIST. A number of large series on patients with GIST is available in the literature from the west while those from the east are very few.

This series on patients with GIST is the largest from India with complete treatment details and survival data.

Methods

The hospital records of 150 patients diagnosed with GIST in Department of surgery, Christian Medical College Hospital, Vellore, between 2007 and 2011 were analysed. Their demographic details including age, gender, clinical presentation, and diagnostic confirmation with biopsy or surgical resection specimen were collected. Findings on imaging including extent of the lesion, operability and multi organ involvement were studied.

Intraoperative details including the extent, completeness of resection, microscopic tumour-free margins were collected. Pathological features including tumour site, size, mitotic index, immunohistochemical staining for CD 117, CD 34, vimentin, smooth muscle actin (SMA), S-100, and desmin were recorded. Tumour risk categorization was defined by using tumour size and mitotic index according to the consensus of the National Institutes of Health (NIH) workshop [4]. The above data were tabulated for each patient. Patients who had operable lesions underwent upfront surgery and followed-up with adjuvant imatinib for high-risk category for 6 months to 1 year.

Patients with inoperable lesions received neoadjuvant chemotherapy with imatinib for 3 to 6 months and were then reassessed with computed tomography for operability.

Postoperative follow-up was done with physical examination, imaging studies like chest X-ray, ultrasound and computed tomography of the abdominal cavity and pelvis. Patients were followed-up in the outpatient clinic. Survival data was obtained from outpatient visits and by sending mails and making phone calls to the patients.

Results

Demographics and Clinical Characteristics

During the period from January 2007 to December 2011, medical records of 150 patients with GIST were studied (Table 1). The age of the patients ranged from 19 to 79 years. The review has shown stromal tumours found to be very less common before the third decade (5 %) and the peak incidence was seen in fifth decade followed by third and fourth decades. Of the 150 patients, 95 were men, and 75 were women. The most common clinical presentation was gastrointestinal bleeding (50 %), followed by abdominal pain (28 %) and abdominal mass (16 %). The other clinical symptoms included generalized weakness, vomiting and anemia for evaluation. Two patients were diagnosed while undergoing routine health check. Four patients had emergency operation for bleeding.

Most of the patients had endoscopic study and biopsy of the lesion. Endoscopic ultrasound was done in cases where endoscopic biopsy was not conclusive or not accessible for percutaneous radiological procedures for biopsy. The imaging modalities used were ultrasound examination (40 %) and contrast-enhanced computed tomography (60 %) of the abdomen and pelvis. Pre-operative needle biopsy was done in those patients who were found to have inoperable tumours (10 %). The most common site of the tumour was the stomach (60 %), followed by small bowel (20 %), duodenum (14 %) and colon and rectum (5 %). Uncommon sites like omentum were involved in one patient. The tumour size ranged from 1 to 30 cm. The majority of tumours were between 5 and 10 cm (50 %) and a significant number of the tumours measured more than 10 cm (25 %).

Table 1 Clinical features

Variables	Number of patients (%)
Age	
<30 years	8 (5.3 %)
30–60 years	111 (74 %)
> 60 years	31 (20.6 %)
Gender	
Male	95 (63.3 %)
Female	55 (36.6 %)
Symptoms	
Abdominal pain	52 (34.6 %)
Melaena	40 (26.6 %)
Mass per abdomen	25 (16.6 %)
Bleeding per rectum	8 (5.3 %)

Histopathological Features

In our series majority of tumours (70 %) were found to have pure spindle cell morphology and less than one fourth of the patients had mixed spindle and epithelioid cell morphology. NIH risk categorization based on the size of the primary tumour and the mitotic index showed one third of the tumours 42/150 (28 %) to be of the high-risk category and among the remaining 35/150 (22 %) were of intermediate-risk and 73 (48.6 %) belonged to the low- and very low risk (Table 2).

Immunohistochemically, CD117 positivity was seen in 135 (90 %), CD34 in 60 %, SMA in 52 (35 %), desmin in 15 (10 %), and S100 in 30 (20 %) of tumours.

Surgical Treatment and Chemotherapy

One hundred and thirty patients had operable tumours at presentation and underwent surgical excision of the tumour (R0 resection). Five patients required adjacent organ resection like spleen, tail of the pancreas and kidney (Table 3). Fifteen patients were found to have inoperable lesion on imaging requiring needle biopsy to confirm diagnosis for purpose of initiating adjuvant treatment. This group of patients received imatinib 400 mg once a day for 3–6 months. In this group, ten patients showed reduction in tumour size with neoadjuvant treatment and subsequently underwent surgical resection. There was complete regression of tumour in one patient while there was progression of disease in four patients.

Most of the patients belonging to the high risk and intermediate category received Imatinib 60/77 and 17 patients did not receive adjuvant therapy due to financial problems (Table 4). Thirteen patients developed recurrence of the tumour while on follow-up and rest of the patients had stable disease. Among these, ten patients were from the

Table 2 Pathological features

Variables	Number of patients (%)
Tumour location	
Stomach	90 (60 %)
Duodenum	26 (17.3 %)
Small intestine	26 (17.3 %)
Colorectal	8 (5.3 %)
Tumour size	
<5 cm	25 (16.6 %)
5–10 cm	67 (44.6 %)
>10 cm	58 (38.6 %)
NIH risk categories	
Low risk	73 (48.6 %)
Intermediate risk	35 (23.3 %)
High risk	42 (28 %)

Table 3 Surgical treatment

Variables	Number of patients (%)
Surgical procedures	
Stomach	
Wedge resection	69 (46 %)
Sleeve gastrectomy	8 (5.3 %)
Subtotal/total gastrectomy	12 (8 %)
Duodenum	
Wide local excision	11 (7.3 %)
Resection and anastomosis	9 (6 %)
Small bowel	
Resection and anastomosis	29 (19.3 %)
Colorectal	
Resection anastomosis	7 (4.6 %)
Multivisceral	5 (3.3 %)
Non-multivisceral	140 (93.3 %)
Surgical margins	
Negative	139 (92.6 %)
Positive	6 (4 %)

group which received adjuvant Imatinib while the other three patients did not receive Imatinib. Four out of ten patients who had regression of the disease following neoadjuvant chemotherapy, surgical resection and on adjuvant chemotherapy, developed recurrence of the disease over a period of 1–2 years while on imatinib. Fifteen patients died during a 2–5-year follow-up. Among the dead, 13 of them belonged to the high-risk category and had recurrence of tumour. Two patients died of cardiac comorbidities.

Follow-up and Survival Analysis

Eighty percent of the patients were followed-up for 1–4 years and 20 % patients were lost to follow-up. The average follow-up period was 24 months. The overall 1- and 3-year survival rates of the 120 patients were 95.8 and 86.6 % (Fig. 1).

Discussion

Mesenchymal tumours are rare tumours of gastrointestinal system. Among mesenchymal tumours, GIST are the most

Table 4 Chemotherapy

Variables	Number of patients	Recurrence
Neoadjuvant	15 (10 %)	7 (46.6 %)
Adjuvant chemotherapy	60 (40 %)	10 (16.6 %)
No chemotherapy	90 (60 %)	3 (0.3 %)

Fig. 1 A survival graph showing the fraction of people in the group surviving over time

common tumours followed by leiomyoma and leiomyosarcoma. The most common site of GIST is the stomach (50–60 %) and small intestine (30–40 %). Five to 10 % of GISTs arise from the colon and rectum. Other less common locations are those outside of the GI tract, like mesentery, retro peritoneum and omentum. The percentage of the site of occurrence of GIST in this present series is comparable to the western literature contrary to previous data from our institution which had shown small bowel to be affected more than the stomach [6].

The most common clinical presentations of GIST were pain and intestinal bleeding, lesions smaller than 2 cm are usually asymptomatic [7]. Significant number of tumours occur in the small bowel and this should be considered as a possible cause of gastrointestinal bleeding when upper and lower GI endoscopy were normal [8].

Imaging studies like ultrasonography and contrast-enhanced abdominal and pelvic CT scan are useful modalities for staging and follow-up. MRI provides better information in staging rectal GISTs. Positron emission tomography CT/MRI is useful for evaluation of tumour response to neoadjuvant or adjuvant chemotherapy.

Most GISTs arising from the intestine are located in the sub mucosal plane. They present as nodular lesions on endoscopic studies. In view of their location, yield from endoscopic biopsy is often very little. When the tumour breaks through the mucosa of the GI tract it may as ulcerated lesion on endoscopy. Endoscopic ultrasound can be used for the precise location and size of the tumour. It is useful to assess the depth and local spread of the tumour. In cases

where tumour presents as sub mucosal nodule, it may be useful to do needle biopsy [9].

Fine-Needle Biopsy

Percutaneous biopsy is not recommended routinely for diagnosis because of the risk of rupturing the tumour, seeding the peritoneal cavity, and bleeding. Tissue confirmation of diagnosis is necessary when the tumour is inoperable and where neoadjuvant chemotherapy is considered and also to exclude other tumours like lymphoma [10].

CT scan or ultra sonogram guided biopsy can be taken from a suspected primary tumour or metastatic lesion [11]. More than 95 % of GISTs are positive for the tyrosine kinase receptor protein KIT, which is detected by the antibody CD117. CD34 60–70 % of GISTs are positive for CD34 and 30–40 % for SMA tumour markers. Only less than 5 % of GISTs are positive for S-100. Unlike other mesenchymal tumours leiomyomas and leiomyosarcomas are positive for SMA and desmin and negative for CD117 and CD34 which helps to distinguish GISTs from other mesenchymal tumours [12]. Around 5 % of GISTs are KIT negative and the presence of PDGFRA protein is used to confirm the diagnosis [13].

Multidisciplinary treatment planning is needed involving pathologists, radiologists, surgeons and medical oncologists in the management of GIST. Staging of the disease is done with chest X-ray, ultra sonogram, or computed tomogram and MRI. MRI is useful in the imaging of rectal GIST.

Treatment

Surgical resection is the mainstay of treatment for GIST because they are resistant to standard chemotherapy and radiation. Surgery is aimed at complete resection of the disease and spillage of tumour should be avoided during operation. Regional lymph node dissection is not routinely required as GIST rarely spread to lymph nodes. Multivisceral resection is recommended when the tumour is adherent to surrounding organs. GISTs are soft and fragile and tumour rupture must be avoided. Tumour rupture is an increased risk for development of peritoneal implantation [14]. Five-year survival after complete surgical resection is around 48–65 % [15]. Palliative resection is performed in large tumours for control of symptoms or complications like bleeding, pain, and other pressure symptoms.

Laparoscopic excision can be done for small lesions but the principles of oncological surgery like grossly negative margins, removal of the tumour without rupture, avoidance of tumour manipulation should be followed. A laparoscopic approach is discouraged for large tumours where microscopic clearance is not possible. The laparoscopic approach significantly decreased length of stay and blood loss [11]. Microscopically positive margins have not been shown to affect survival, and management should be individualized in terms of re-resection [16].

GISTs located in the proximal stomach, especially on the greater curvature, may be amenable to wedge resection or tangential resection. Imatinib mesylate is a selective inhibitor of tyrosine kinases of PDGFR and of c-kit receptor. Adjuvant imatinib treatment after surgical resection is beneficial in high-risk tumours to prevent recurrence. In recurrent, metastatic, or inoperable lesions, use of imatinib has shown response in 50 % patients and 75–85 % had stable disease [17].

In patients with unresectable tumour and metastatic disease, neoadjuvant chemotherapy with imatinib is given for 6 months to 1 year for tumour reduction followed by surgical resection. All patients with intermediate, high-risk tumours, and metastatic patients, who have been completely relieved of all lesions surgically, were given adjuvant imatinib for 1 to 3 years [11].

The standard dose of 400 mg daily of imatinib for 6 to 12 months and no benefit with higher dose of 800 mg/day has been found except in patients with exon 9 KIT mutations. Primary resistance to imatinib is known to occur (i.e., disease progression within 6 months of treatment) and secondary resistance (progression after 6 months after evidence of initial effectiveness) occurs more often, with an average time to progression of 20 months [18]. It is believed to occur through development of a secondary acquired KIT mutation [19]. Sunitinib another molecule inhibitor of receptor tyrosine kinases has been shown to be an effective second-line therapy for patients with GISTs [20, 21].

Surgical Treatment of Metastatic GIST

Surgical resection in patients with metastatic disease has been considered. Patients also may benefit from surgical resection of remaining gross disease to improve progression-free survival and prevent development of secondary resistance, because remaining tumour harbor cells are capable of undergoing mutation and are the clones presumed to be resistant to therapy [22]. Surgical resection includes removal of all gross disease and may need multivisceral resection and omentectomy. Liver resection is not advisable as secondaries often involve both the lobes. Surgical therapy may be especially appropriate for patients who do not have access to second-line inhibitor of receptor tyrosine kinases further medical therapy [23].

Follow-up

High-risk patients generally relapse within 2 to 3 years, while low-risk patients may take longer periods for the disease to relapse, although much less likely [24]. The routine follow-up schedules vary from institution to institution. In general, intermediate and high-risk patients are advised follow-up with CT scan every 3–4 months for 3 years, then every 6 months until 5 years and yearly afterwards; for low-risk tumours, follow-up is carried out with CT scan every 6 months for 5 years. Very low-risk patients may not need routine follow-up, although they must be aware that the risk is not nil [24].

Conclusion

Gastrointestinal stromal tumours are the common mesenchymal tumours of the gastrointestinal tract. They are more common in the fourth and fifth decades, and predominant in males. Intestinal bleeding and mass abdomen are the most common presentation. Surgical treatment is the best treatment for operable lesions. KIT tyrosine kinase inhibitor like imatinib is useful for neoadjuvant treatment in inoperable or metastatic diseases which showed significant reduction in tumour size. Imatinib therapy had shown stable disease and reduced tumour recurrence [25]. Regular follow-up with ultra sonogram and computed tomogram help to diagnose tumour recurrence. Sunitinib, a multitargeted TKI, is useful in case of imatinib resistance.

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