Abstract

Introduction
Gastrointestinal stromal tumour is a rare mesenchymal tumour of the gastrointestinal tract. The stomach and small intestine are the favoured sites for these tumours. Pre-operative diagnosis is difficult on clinical basis for such tumours and only a detailed histopathological examination of specimen reveals its true nature. The aim of this research study was to examine abdominal gastrointestinal stromal tumour in a general surgery ward.

Materials and methods
A retrospective case review study of patients, who had a diagnosis of the abdominal gastrointestinal stromal tumour, was performed. Clinical presentation, operative findings and a follow-up was recorded for these patients. Recurrence and development of a new tumour was recorded during the follow-up.

Results
Twelve patients, who had an abdominal gastrointestinal stromal tumour, were examined. There were nine male patients and three female patients. Eight patients were diagnosed with an abdominal mass, one patient had peritonitis, one patient had an upper gastrointestinal bleeding, one patient had rectal bleeding and one patient was diagnosed with an intestinal obstruction. All the patients had exploratory laparotomy and post-operative imatinib was given to them.

Conclusion
Gastrointestinal stromal tumour in the abdomen is a rare cancer. These tumours have variable clinical behaviour, with abdominal mass being the common symptom. Surgical resection with negative margin is the preferred modality of treatment for gastrointestinal stromal tumour.

Introduction
Gastrointestinal stromal tumour (GIST) represents a rare mesenchymal tumour of the gastrointestinal system. Overall, the GISTs comprise of 5% of sarcomas. GISTs tend to have low-growth rates, with a subsequent long time for the development of symptoms. Their origin is by differentiation of intestinal pacemaker cell, known as interstitial cells of cajal. Gastrointestinal cells are now defined as spindle cells, epithelioid cells or occasionally pleomorphic tumour of the gastrointestinal tract without smooth muscle or Schwann cell differentiation. Immunohistochemical marker ‘c-kit receptor’ (CD117) or the platelet-derived growth factor receptor A (PDGFRA) mutations, identify these cells, which are most specifically diagnostic markers, available currently. Gastrointestinal stromal tumours have variable clinical behaviour, with abdominal mass being the common symptom. Surgical resection with negative margin is the preferred modality of treatment for gastrointestinal stromal tumour.

Materials and methods
This research work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee associated to our institution in which it was performed. All subjects gave full informed consent to participate in this study.

A retrospective case study of 12 patients, who had abdominal GIST, was performed from 2008 to 2011. Patients with abdominal sarcoma were excluded from this study. A detailed review of an each patient’s records in terms of clinical history, examination and radiological investigation, were studied. Surgical procedure was performed and the pre-operative findings were recorded in terms of size, site, location and any presence of metastasis. Histopathology of the specimen and immunohistochemical markers, were used for confirmation of the diagnosis of GISTs. Each patient had a regular follow-up.

Results
Out of 12 male patients, there were nine male patients and three female patients. The age of the patients ranged from 9–60 years. Eight patients presented with a painless abdominal mass, one patient had an intestinal obstruction (jejunum) and two patients had peritonitis (rupture of ileal tumour). The tumour in eight patients was the located in the stomach, three patients had it in the small gut and one patient had it in the rectum (Figure 1). Reactive lymph-node hyperplasia was present in three patients. The size of the tumour ranged from 3–16 cm. The maximum size of tumour was present in a gastric lesion (16 cm). Pre-operative diagnosis was performed in four patients, of our series in this
Research study

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In this series of the research study, by fine-needle aspiration cytology study. Emergency laparotomy was performed in three patients, one patient had features of peritonitis and another patient had features of intestinal obstruction. In this series of the research study, each patient had laparotomy and wide resection of about 2.5 cm from tumour margin. One patient had the partial resection of omentum due to adhesions of tumour that activated the omentum and the other patient had resection of bladder cuff, which had a small gut tumour adherent to the bladder wall. No liver metastasis was observed in any patient. Histopathological examination was found to be consistent with a diagnosis of GIST (Figure 2).

Immunohistochemical marker CD117 confirmed the diagnosis of GIST. Surgery was followed by oral intake of imitinab. Follow-up of average years was recorded for the patients with GIST. Recurrence was observed in six patients, after a mean follow-up period of 19 months. One patient had a gastric tumour, one patient had a jejunal tumour (rupture of the tumour) and rectal GIST and two patients had ileal GIST. Three patients had >5 mitoses/50 high power fields (HPFs), first patient had a gastric tumour (16 cm), the second patient had a rupture of tumour and the third patient had a rectal gastric GIST. All these three patients were managed by chemotherapy. One patient died after 16 months of follow-up.

Discussion
GISTs represent a heterogeneous group of non-epithelial neoplasms, with simple or epithelioid cells, which display a range of differentiation. Risk factors and aetiology remains undetermined. As per the diagnostic criteria, GISTs are defined as gastrointestinal mesenchymal tumours, expressing a proto-oncogene protein called CD117, detected by immunohistochemistry. GISTs are most commonly located in the stomach (70%) followed by small intestine (20%), colon and rectum (5%) and oesophagus (5%). GISTs develop rarely in the retroperitoneum, omentum or the mesentery. The prevalence of GIST is higher, because many patients live years, often large tumours are present, and without any overt manifestations. Less than 5% of GISTs are associated with one of the three tumour syndromes, in order of decreasing frequency as follows: neurofibromatosis type 1 (NF-1), Carney’s triad and familial GIST syndrome. There is a rare entity called Carney’s triad, which occurs predominantly in young women, characterised by gastric GIST, paraganglioma and pulmonary chondroma. There is an existence of familial GIST syndrome, and till date 12 families with familial GIST have been reported, in the published literature, with autosomal dominant transmission of mutation manifesting afterwards in middle age.

The signs and symptoms of GIST depend on the tumour size and its location. Many GISTS are found to be asymptomatic. The tumour is found incidentally, during specific radiological investigations or laparotomy for other conditions, and clinical presentation of GIST, in order of frequency, includes gastrointestinal bleeding, palpable mass or abdominal pain and bowel obstruction. The perforation of tumour presents as an acute abdomen. A pre-nucleated tumour can undergo twist and lead to pain in the abdomen. Sometimes, there can be an extraluminal tumour leading to volvulus of the gut and present as an acute emergency. Abdominal mass can be mobile or fixed depending on location of the tumour in the abdomen. Adhesions with surroundings restrict the mobility of the abdominal mass. Consistency of the occurrence of GIST is firm and is often smooth surfaced. Sometimes a mobile tumour can reach the pelvis and mimic as pelvic mass. Obstruction can result from intraluminal growth of an endophytic tumour or from luminal compression from an exophytic lesion. Size of the lesion varies from a few millimetres to over 40 cm. These tumours arise from the muscularis mucosa or muscularis propria layers and most of them exhibit an endophytic growth pattern. The overlying mucosa is usually preserved, but larger and more aggressive tumours tend to ulcerate through overlying mucosa. Ulceration is observed in gastric GIST, where often large tumours are present, and

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this ulceration presents as abdominal pain and gastrointestinal bleeding. A gastric tumour can sometimes invaginate into duodenum and can present as a gastroduodenal intussusception. Presentation of the gastric GIST as a polyp is rarely observed. A small-gut GIST has an associated NF-1, with neurofibroma observed on the abdomen, as well as on the gut. The frequency of benign versus malignant GISTs varies between the sites. Benign GISTs outnumber the malignant GISTs in the stomach, whereas malignant GISTs are more common in the intestines. The GISTs that have metastasised at presentation have a very poor prognosis. Both bone and lung metastases occur rarely. Tumours in the small intestine are known to behave most aggressively than those in the stomach. Metastasis at the time of presentation and primary seeding at the time of primary operation, both have very poor prognosis.12,13. Lymphadenopathy is characteristically absent and it is difficult to differentiate GISTs from lymphoma, metastasis or an adenocarcinoma. The sonographic features of the GIST are echo-poor, with cystic and necrotic changes14. Computerised tomography (CT) and magnetic resonance imaging (MRI) scans reveal GIST as a heterogeneous mass, with central necrosis and a large extraluminal component, severe haemorrhage within the mass associated with hypervascular stromal tumour. A crescent-shaped necrosis in the peripheral aspect of the extraluminal lesion suggests the presence of the stromal tumour15. CT findings that favour malignant stromal tumour include the following, size >5 cm, lobulation, heterogeneity with central necrosis, mesenteric infiltration, lymphadenopathy and exophytic growth. Multidetector CT scan can detect most lesions of size >2 cm. An MRI scan is useful in delineating the tumour, defining its relationship and in detecting both haemorrhage and necrosis. Positron-emission tomography (PET) scanning has recently been touted as an excellent study for detecting the metastatic disease of GIST. PET scanning has also been used to monitor responses to adjuvant therapies, such as imatinib mesylate. Angiography is rarely used in the diagnosis or management of the GISTs. It may be used during diagnostic dilemmas or for urgent treatment of complications such as gastrointestinal haemorrhage. Cellular morphology as visualised by light microscopy can be variable. Histopathological examination of tumour reveals combination of spindle and epithelial cells.16. The indicator of GIST is the expression of the c-kit (CD117), which is a transmembrane receptor, with a component of tyrosine kinase, is present in 94% of these tumours, and about 3%–5% of the remainder of kit-negative GISTs contain PDGFRA alpha mutations16. Vimentin, a type III intermediate filament protein, expressed in mesenchymal cell, is present in all GISTs. CD34, another transmembrane protein, is observed in 50%–70% of the GISTs. In approximately, 60% of cases of GISTs, mutations in the kit gene are found in the juxtmembrane domain (domain 3). The reported rate of these mutations ranges from 21%–88%.5,17.

Mutations of c-kit have been shown to be associated with malignancy. Genetic markers, including deoxyribonucleic acid (DNA)-copy number changes, telomerase activity and kit mutation status, are useful in more accurately identifying tumours with malignant potential. In contrast to adults, children with GIST lack mutations in kit or PDGFRA. These mutations cause the receptor to be activated constitutively without its ligand. GISTs with mutant kit are more likely to be high-grade tumours, characterised by more frequent recurrences and a higher mortality rate than GISTs with normal kit. A variety of features, including histologic-grade mitotic index and other markers of proliferation, size and histologic pattern have demonstrated prognosis in a small series, but nothing has been shown to be an independent indicator. Less than 3% of tumours are <10 cm and with fewer than 5 mitoses/50 HPFs metastasised, whereas 86% of tumours are >10 cm and >5 mitoses/50 HPFs metastasised. However, tumours >10 cm with mitotic activity <5/50 HPFs and those <5 cm with mitotic activity >5/50 HPFs, had a relatively low-metastatic rate. This location of tumour is not considered a significant prognostic factor. There is no correlation of symptoms with prognosis.

The primary treatment of GIST is a surgical resection with a negative tumour free margin of at least 2 cm is recommended18,19. A meticulous surgical technique is necessary to avoid intra-operative tumour rupture, which is associated with a poor prognosis. Gastric GIST can require gastrectomy, sometimes depending on location, size and any pre-operative diagnosis. Patients with rupture of gastrointestinal tumour, usually have poor prognosis due to tumour spill. Usually, only a wedge or segmental resection of the underlying organ is required, because GISTs tend to protrude from the tissue of origin and displace surrounding structures, unlike other intra-abdominal malignancies, which are often invasive. Rarely, these can infiltrate surroundings, as in our case, one duodenal GIST had infiltration to omentum and one ileal GIST had infiltration into the bladder wall. Omentectomy and the local excision of bladder cuff were performed for this local infiltration. Consequently, negative surgical margins are usually attained. However, the importance of the negative microscopic margins on the resected organ is dubious, when there is a massive (e.g., 15 cm) GIST that is free to shed cells throughout the abdomen. Hence, a metastatic or residual disease requires medical management. Treatment with imitinab results in a 60%
remission rate and 85% of overall control rate. Overall, in about two out of the three patients treated, the tumours shrink by at least half the original size. In a small number of patients, there is a mild shrinkage or at least no further growth. About 15% of patients get worse in spite of getting imatinib. A newer drug called imatinib is very helpful for many patients with advanced-stage GIST, and this drug may help the earlier-stage tumours to shrink. This drug targets both the kit protein and the PDGFRA protein, blocking their ability to cause tumour cells to grow and divide. Flavopiridol, a natural product-based compound, which is being investigated as a cancer drug, represents a possible new treatment for GIST. Our results indicate that targeting kit expression and these anti-apoptotic proteins with flavopiridol represents a novel means to disrupt GIST-cell dependence on kit signalling and collectively renders these cells sensitive to apoptosis. It inhibits total kit expression, which lowers the amount of kit protein that is being produced. Flavopiridol may serve as an alternative to the receptor-targeted approaches used to treat GIST tumours and other kit-dependent malignancies. External beam radiation is generally not indicated in patients with metastatic GIST, because of the diffuse distribution of the recurrent disease that typically occurs within the liver or peritoneum. When radiation is used, it is strictly used for palliation. It can reduce pain or discomfort associated with a liver metastasis or pelvic recurrence. Occasionally, it may also be used to control bleeding from a peritoneal recurrence that causes gastrointestinal bleeding. Hepatic artery embolisation is an effective palliative therapy for patients, with liver metastases from GIST, because the tumours tend to be hypervascular and derive most of their blood supply from the hepatic artery. There are also newer methods to treat cancers that have spread to the liver. These treatments may include cryosurgery (freezing the tumour), radiofrequency ablation (RFA) probe, embolisation, or ethanol ablation. These methods do not require a surgical operation. The freezing probe, RFA probe or needle is inserted through the skin and guided to the tumour by CT scans or ultrasound images. The significance of these treatments in patients with GIST is not fully known, because not enough studies have focused on this rare type of cancer.

**Conclusion**

GISTS are uncommon with myriad of clinical manifestations, with male predominance. Pre-operative diagnosis of GIST is difficult and the clinical experience, with detailed histopathological examination of the specimen confirms the diagnosis of GIST. Wide local resection of the tumour is curative. Locoregional metastasis and patients, who had rupture at the time of the GIST presentation experienced more recurrence than those with no occurrence of metastasis.

**Abbreviations list**

CT, computerised tomography; GIST, gastrointestinal stromal tumour; HPF, high power fields; MRI, magnetic resonance imaging; NF-1, neurofibromatosis type 1; PDGFRA, platelet-derived growth factor receptor A; PET, positron-emission tomography; RFA, radiofrequency ablation.

**References**

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