

Gastro-intestinal stromal tumours (GISTs) – the Pretoria experience and a literature review

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Summary

Aim. To analyse the presentation and management of patients with gastro-intestinal stromal tumours (GISTs) at Pretoria hospitals.

Design. A retrospective study was done in which all available clinical records of primary c-KIT positive GISTs were analysed.

Setting. Secondary and tertiary care institutions in Pretoria, including both private and public hospitals.

Subjects. The population studied included all individuals treated at Pretoria hospitals from 17 July 2000 to 1 April 2009 who had a GIST confirmed with immunohistochemical c-KIT staining. Patients with incomplete or inaccessible clinical records were excluded.

Outcome measures. Patient demographics including gender, age and race; presenting symptoms and signs; results of special investigations; and treatment.

Results. Fifty-four cases were identified for inclusion in the study. The age of the subjects ranged from 15 to 83 years. The male-to-female ratio was 1.5:1. The organ most commonly affected was the stomach, and abdominal pain and weight loss were the most common presenting symptoms. Seventy-six per cent of the patients were treated surgically, and 24% received imatinib.

Conclusion. GISTs often present late with nonspecific symptoms, and are frequently discovered incidentally. Large tumours tend to be malignant.

Gastro-intestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastro-intestinal tract (GIT).¹⁻³ They are, however, rare and account for about 1% of all gastro-intestinal (GI) tumours.^{1,4,5}

GISTs originate from the interstitial cells of Cajal (ICC), an intestinal pacemaker cell. GISTs express the KIT protein (CD117) or CD34, and it is this feature that distinguishes them from leiomyoma and leiomyosarcoma. The diagnosis is made by immunohistochemical staining techniques for c-KIT.^{6,7} About 3 - 5% of GISTs are KIT-negative.

The incidence of GISTs is estimated to be 6 - 20 cases per million people per year.^{1,8} They occur at any age, but the highest incidence is in individuals of 40 - 80 years of age.⁶ No risk factors for developing these tumours are known.⁵ The male-to-female ratio is 1:1, but some studies suggest a slight male predominance.^{1,9} They occur equally in all races.^{1,5}

Sixty to seventy per cent of GISTs arise in the stomach, 10 - 30% in the small intestine, 10% in the colon and ano-rectum, and

1 - 5% in the oesophagus. Rarely, they are found outside the GIT, e.g. mesentery, omentum, retro-peritoneum, uterus, vagina and prostate.⁸⁻¹²

Macroscopically, GISTs vary in size from a few mm to >30 cm. They usually develop from the outer smooth muscle layer of the GIT.^{8,11} Histologically, they vary from cellular spindle cell tumours to epithelioid and pleomorphic cell types.^{8,11} These tumours may be benign or malignant. Tumour size (>5 cm) and mitotic index (>1 - 5 mitotic figures/10 high-power fields (HPFs)) are the most reliable predictors of biological behaviour.^{1,3}

Ten to thirty per cent of GISTs are malignant.^{1,10} GISTs mainly metastasise to the liver (50 - 60%) and peritoneum (20 - 43%). Metastases to other sites (e.g. lung, bone and lymph nodes) are rare.^{8,9}

The treatment of choice is wide local excision. Complete resection of the tumour offers the only chance of cure. Fifty per cent of GISTs recur even after apparent complete resection.^{9,12}

GISTs are resistant to both conventional radiotherapy and chemotherapy.¹⁴ Imatinib mesylate is a tyrosine-kinase inhibitor with potential for treating malignant, metastatic and/or unresectable GISTs.¹⁴

The prognosis of low-grade GIST is very good after complete resection, with a 5-year survival rate of 95%. Malignant GISTs have a 5-year survival rate of 0 - 30% without adjuvant/neo-adjuvant imatinib treatment. With imatinib, survival is improved, but no long-term data are currently available.¹

Methods

Three pathology laboratories (the Institute for Pathology, University of Pretoria, Drs Du Buisson and Partners, and Lancet Laboratories) searched their records on our behalf for cases confirmed with c-KIT positive GISTs. Eighty-three cases were found from the records of secondary and tertiary care institutions in Pretoria, including both private and public hospitals (Table I). Access to the clinical records of these patients was requested from the superintendents of Steve Biko Academic Hospital and Kalafong Hospital and the surgeons in private practice who treated these cases. In 29 cases (10 females and 19 males), the records were either unavailable, lost, incomplete or access to them was denied. The records of the remaining 54 cases were analysed.

The outcome measures were patient race, age, gender, presenting symptoms and signs, special investigations and treatment. All the results were expressed as a percentage of the total number of patients studied, and these were compared to and contrasted with the data given in the current literature.

TABLE I. INSTITUTIONS FROM WHICH CASES WERE TAKEN

Kalafong Hospital
Montana Hospital
Steve Biko Academic Hospital
Unitas Hospital
Wilgers Hospital
Zuid-Afrikaanse Hospital

TABLE III. BIOLOGICAL BEHAVIOUR OF THE TUMOURS

Biological behaviour	No.	Percentage	>8 cm	≥3 mf/10 HPF
Malignant course	21	39	18	11
Apparently benign course	28	52	0	1
Undetermined	5	9	2	3

mf = mitotic figures; HPF = high-power field.

Results

Between 17 July 2000 and 1 April 2009, 54 cases of GIST with accessible and complete clinical records were identified.

Ages of patients

The ages varied from 15 to 83 years. The median was 49 years and the average 56 years. Eighty per cent of the subjects were between 40 and 80 years of age.

Race

There were 22 black and 32 white patients in our series. No coloured or Asian patients were in the study group.

Metastases

Anatomical sites affected are shown in Table II. Eleven patients had confirmed metastases – 7 hepatic, 3 hepatic and peritoneal, and 1 lung metastasis.

TABLE II. ANATOMICAL SITE AFFECTED

Organ	No. of cases	Percentage
Oesophagus	5	9
Stomach	40	74
Small intestine	5	9
Colon	0	0
Ano-rectum	2	4
Other	2	4
Total	54	100

Pathology

Tumour size was known in 30 of 54 cases, and ranged from 0.6 x 0.5 x 0.4 cm to 30 x 28 x 18 cm. Tumours larger than 8 cm frequently had a malignant course (Table III).

Mitotic figures varied from 0 to 22 per 10 high-powered fields.

Forty (76%) of the tumours consisted of spindle-shaped cells, and 5 (9%) of epithelioid cells. The remaining 8 (15%) had both spindle and epithelioid cells.

Presenting symptoms

The most common presenting symptoms were: abdominal pain – 57%; weight loss – 26%; heartburn – 17%; vomiting – 17%;

fatigue – 13%; melaena – 13%; epigastric discomfort – 11%; and haematemesis – 11%.

Clinical signs

The most common presenting clinical signs were: pallor – 35%; palpable abdominal mass – 28%; abdominal distension – 22%; abdominal tenderness – 15%; ascites – 9%; and cachexia – 9%.

Blood test

The most common haematological abnormality found in GIST patients was anaemia.

Ultrasound

Sixteen patients had abdominal ultrasound scans; mass lesions were detected in 8.

Computed tomography (CT) scan

Eighteen patients had CT scans, in whom 13 gastric tumours were demonstrated; 4 of these patients also had liver metastases. One oesophageal and 1 prostatic GIST were also found.

Endoscopy

Thirty-eight patients underwent endoscopic investigations which revealed that 26 had gastric tumours, 2 had gastric ulcers, 3 had oesophageal tumours, 1 had a tumour in the distal duodenum, and 1 rectal mass was demonstrated.

Treatment

Forty-one (76%) of the 54 cases had surgical treatment (Table IV).

Discussion

The age incidence in our study was as described previously: 80% of patients were in the age group 40 - 80 years. The median age was 49 years, which was about 10 years less than the average of 60 years previously reported.^{1,4}

There was a significant male predominance in our series, with a male-to-female ratio of 1.5:1.^{1,8,9}

There were 22 black and 32 white patients in our study group. We postulated that this curious result was the consequence of the white group being more frequently subjected to endoscopic investigation for unrelated conditions, e.g. gastro-oesophageal reflux disease. Supporting this postulate is the fact that the 15 subjects with small GISTs that were incidentally detected during such a work-up were all white.^{1,3,5}

TABLE IV. NUMBER OF CASES THAT RECEIVED SURGICAL TREATMENT – COMPLETE AND INCOMPLETE RESECTION

Complete resection	No. of cases	Percentage
Gastric wedge resection	6	11
Subtotal/total gastrectomy	8	15
Gastrectomy and hepatectomy	1	2
Endoscopic resection of gastric GISTs	13	24
Laparoscopic resection of gastric GISTs	1	2
Small bowel resection and primary anastomosis	4	7
Rectal resection	2	4
Thoracotomy and resection of oesophageal tumour	1	2
Subtotal	36	67
Incomplete resection		
Gastric wedge resection, liver metastases not resected	2	4
Debulking of large gastric GIST	1	2
Debulking of retro-peritoneal GIST	1	2
Thoracotomy and biopsy of oesophageal GIST with lung metastases	1	2
Subtotal	5	10
Total	41	76

Gastric GISTs represented 74% of our cases (Table II), a somewhat higher percentage than previously reported. Nine per cent of our GISTs were of small-bowel origin. Oesophageal GISTs contributed 9% to our total, which was almost double the 5% reported in the literature. Four per cent of our cases were from sites outside the GIT.⁹⁻¹¹

A tumour size >8 cm correlated well with a malignant course. Occasionally, smaller tumours were also aggressive. The mitotic index varied from 0 to 22 mitotic figures per 10 HPF. In our experience, >3 mitoses/10 HPF was a strong predictor for malignancy.^{7,8,10} Seventy-four per cent of our GISTs consisted of spindle-shaped cells, and the remainder consisted of epithelioid cells and combinations of both cell types. As previously confirmed, we found no correlation between predominant cell type and the biological behaviour of the GIST.^{5,6}

Thirty-nine per cent of our GISTs were obviously malignant, 48% were apparently benign and, in 13% of cases, the diagnosis was undetermined. The incidence of malignant GISTs was higher in our series than that described in the literature. Some of the undetermined cases were probably malignant too but, because of the early postoperative deaths of these patients, no definitive diagnoses were made. Our follow-up time was also too short to confidently exclude malignant disease in all of the apparently benign cases. When tumour size and mitotic rate were combined to pre-

dict the biological behaviour of a GIST, it was done accurately in 85% of cases.⁵⁻⁸

The most common presenting symptoms of our patients were abdominal pain – 37%, weight loss – 26%, heartburn – 17%, vomiting – 12%, melaena – 13%, and fatigue – 13%. Only the fifth most common symptoms (melaena and fatigue) correlated with internal haemorrhage; the other symptoms were nonspecific.^{4,5,13}

The most common clinical signs at presentation were pallor, palpable abdominal mass, abdominal distension and tenderness. Clinical anaemia correlated with internal haemorrhage, but the other signs were again nonspecific.^{4,5,13}

Sixteen of our patients had an abdominal ultrasound scan, in 8 of whom a mass lesion was seen, which is a positive yield of 50% of examinations done.

Thirty-seven of our patients had gastroscopy; in 34 cases, a lesion was detected.

Eighteen patients had CT scans, of which 15 were abdominal scans. Thirteen of these revealed a gastric tumour, and 4 patients were also diagnosed with hepatic metastases.

Two thoracic CT scans were done; 1 showed a posterior mediastinal mass. One pelvic CT was done and demonstrated a pelvic tumour of prostatic origin. The special investigations employed and the results correlate with those in the literature.^{1,8}

Forty-one (76%) of the 54 patients underwent surgery. Thirty-six (67%) had a complete resection, which compared favourably with the figure of 40 - 60% in the literature.³ In 13 (24%) of these cases, small incidental GISTs were found on endoscopy and removed at the same time.

Only 13 patients (24%) were referred for imatinib therapy (7 had adjuvant therapy, 2 neo-adjuvant therapy, and 4 received palliative imatinib) (Table V). Considering the overall 5-year survival of 50%, it is our opinion that imatinib has been underutilised to date in our setting. Our recommendation would be that, in future, all confirmed GIST patients be given imatinib, be it palliative or as an adjuvant therapy.

TABLE V. NON-SURGICAL THERAPY

Imatinib therapy	No. of cases	Percentage
Neo-adjuvant therapy	2	4
Adjuvant therapy	7	13
Palliative therapy	4	7
Total	13	24

Conclusion

GISTs are rare tumours among our patient population. Patients present with nonspecific symptoms and signs, and GISTs are frequently discovered incidentally (28%). With few exceptions, our findings corresponded with those in the literature. The most notable exceptions included a significant male predominance in our series, the unusually high incidence of oesophageal GISTs, and the relatively high incidence of malignant GISTs. We observed a marginally higher incidence of gastric GISTs than described elsewhere, and our median age at presentation was 10 years younger than described in other studies. We found that biological behaviour could be predicted with a high degree of accuracy when mitotic

rate and tumour size were considered in combination, although occasional errors did occur.

We would ideally like to see imatinib being used in future in all cases of a GIST.

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REFERENCES

- Gupta P, Tewari M, Shukla HS. Gastrointestinal stromal tumour. *Surg Oncol* 2008;17(2):129-138.
- Blum MG, Bilimoria KY, Wayne JD, et al. Surgical consideration for the management and resection of esophageal gastrointestinal stromal tumours. *Ann Thorac Surg* 2007;84:1717-1723.
- Samelis GF, Ekmektzoglou KA, Zografos GC. Gastrointestinal stromal tumours: Clinical overview, surgery and recent advances in Imatinib mesylate therapy. *Eur J Surg Oncol* 2007;33:942-950.
- Hopkins TG, Marples M, Stark, D. Sunitinib in the management of gastrointestinal stromal tumours. *Eur J Surg Oncol* 2008;34(8):844-850.
- Madeiras F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors. *Am J Surg Pathol* 2004;28(7):889-894.
- Somerhaus N de Saint Aubain, Fletcher CDM. Gastrointestinal stromal tumours: an update. *Sarcoma* 1998;2:133-141.
- Rader AE, Avery A, Wait CL, et al. Fine-needle aspiration biopsy diagnosis of gastrointestinal stromal tumours using morphology, immunocytochemistry, and mutational analysis of c-kit. *Cancer* 2001;93(4):269-275.
- Stamatakis M, Douzinas E, Stefanaki C, et al. Gastrointestinal stromal tumour. *World J Surg Oncol* 2009;7:61. Published online 1 August 2009. doi: 10.1186/1477-7819-7-61.
- DeMatteo R, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumours recurrence patterns and prognostic factors for survival. *Ann Surg* 2000;231(1):51.
- Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumours: a review. *Eur J Cancer* 2002;38:39-51.
- Mukherjee S, Sawyer MAJ, Decker RA. Gastrointestinal stromal tumours. Medscape Reference. <http://emedicine.medscape.com/article/179669-overview> (accessed 4 February 2010).
- Coffey RJ, Washington MK, Corless CL, et al. Menetrier disease and gastrointestinal stromal tumours: hyperproliferative disorders of the stomach. *J Clin Invest* 2007;117(1):70-80.
- Davis AR, Ahmed W, Purkiss SF. Port site metastasis following diagnostic laparoscopy for a malignant gastro-intestinal stromal tumour. *World J Surg Oncol* 2008;6:55.
- Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to Imatinib in advanced gastrointestinal stromal tumours are predicted by different prognostic factors: A European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australian Gastrointestinal Trails Group Study. *J Clin Oncol* 2005;23:5795-5804.
- Demetri GD, Von Mehren M, Blake CD, et al. Efficacy and safety of Imatinib mesylate in advanced gastrointestinal stromal tumours. *New Engl J Med* 2002;347:472-480.