Gastrointestinal stromal tumours: Our experience

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Abstract

Background Gastrointestinal stromal tumours (GIST) are histologically heterogeneous group of mesenchymal tumours arising in gastrointestinal tract (GIT), though they represent only 0.2% of all GI tumours. The advent of effective chemotherapy for GIST has altered but not diminished the role of surgery which remains the standard therapy for all resectable non-metastatic tumours.

Purpose To present our experience of management of GIST which are most common sarcomas of the GIT, commonly seen in stomach and small bowel.

Methods All cases of GIST managed at our centre from April 2006 to June 2008 were included in the study.

Results Thirteen cases of GIST were operated in the study period. Commonest presenting symptoms were, lump abdomen and dull abdominal pain. After initial USG, CECT was done in all cases. Tumour was seen to arise from small bowel (7/13), stomach (4/13) and one each from oesophagus and omentum. Resection and anastomosis was done in (12/13) cases, one case was inoperable at surgery. Histopathological examination confirmed GIST in all. Immunohistochemistry studies were done in 4/13 cases. 2/13 patients required postoperative chemotherapy.

Conclusion GIST has varied presentation as shown by our study. All patients require accurate delineation by CECT scan and individualised management. Immunohistochemistry should be done in all, and those who are in high risk group, metastatic or unresectable require imatinib mesylate. Patients who are CD117 positive show good response to imatinib mesylate. Six monthly follow up is recommended with USG/CECT.

Keywords GIST · CD117 · Imatinib · Mesylate

Introduction

Gastrointestinal stromal tumours (GIST) are a histologically heterogeneous group of mesenchymal tumours that arise in the gastrointestinal tract (GIT). They are the most common sarcomas of the GIT commonly seen in stomach and small bowel, though they represent only 0.2% of all GI tumours [1]. These tumours were thought to be of smooth muscle origin and due to its uncertain prognosis, the term ‘STUMP’ (smooth muscle tumours of uncertain malignant potential) was used. They were also called ‘GANT’ (gastrointestinal autonomic nerve tumours) because of the similarity of their cells to neural cells in the autonomic myenteric plexus [2, 3]. The term GIST was previously used to describe any mesenchymal tumour of GIT [4]. GIST is currently defined as CD117 positive (more than 10% tumour cells positive), spindle cell or epithelioid cell neoplasms [5, 6]. GISTs are mostly clinically silent until they grow large, bleed or rupture [7, 8]. GIST may be detected incidentally following endoscopy, imaging or surgery in about 41–63% cases [9, 10]. A dramatic change in the treatment of GIST occurred following the recognition that

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activated KIT provided the driving force for GIST growth, and this led to the use of imatinib mesylate (Gleevec/Glivec) as targeted therapy. The advent of effective chemotherapy for GIST has altered but not diminished the role of surgery which remains the standard therapy for all resectable non-metastatic tumours. Guidelines for chemotherapy have been changing. Currently as per NCCN 2008, chemotherapy has been recommended in a postoperative setting for intermediate and high risk groups following curative resection. The 5-year overall survival rates following complete resection of localised GIST, range from 40 to 55% [11, 12]. Controversy exists over conservative management of small sized tumours, however the recognition that even small sized GIST can exhibit aggressive behaviour, leads most surgeons to recommend excision of all tumours, in patients who are acceptable operative candidates.

Materials and methods

We studied all cases of GIST managed at our centre from April 2006 to June 2008. All patients were evaluated by clinical examination and by imaging, using USG abdomen initially followed by CECT abdomen, besides immunohistochemistry studies in last four cases as the same was not available earlier. All patients were offered surgery as the primary modality of treatment. Patients who were in the high risk group (NCCN 2007) and those positive for CD117 were offered postoperative chemotherapy in the form of imatinib mesylate. Patients were kept on regular follow up with 6 monthly clinical examination and USG abdomen.

Results

Thirteen cases of GIST were operated in the study period. Mean age at presentation was 46.2 years (28–70 years); male-to-female ratio was 10:3. Presenting symptoms were lump abdomen and dull abdominal pain in nine cases, recurrent lower GI bleed in one case, anaemia in one case, incidental in one case and malena in one case. After initial USG evaluation, CECT was done in all cases for better localisation. At surgery, tumour was seen to arise from small bowel in 7 out of 13 cases (duodenum – 1, jejunum – 3, ileum – 3), from stomach in 4 out of 13 cases (Fig. 1) and one each from oesophagus and omentum (Fig. 2). Resection and anastomosis was done in 10/13 cases (Fig. 3), one case of posterior wall stomach GIST underwent sleeve resection, omental GIST underwent omentectomy and one case was found to be inoperable at surgery as the tumour was encasing the superior mesenteric artery pedicle and splenic vein, and infiltrating into pancreas and retroperitoneum. Histopathological examination confirmed diagnosis of GIST in all cases. Immunohistochemistry studies were done in last four cases out of the 13 cases.

Fig. 1. Stomach GIST (resected specimen)

Fig. 2. Omental GIST

Out of the 13 cases, one case was in the high risk group and one case was unresectable. Both of these patients were offered postoperative chemotherapy in the form of imatinib mesylate conforming to NCCN 2007 guidelines. On follow up, the patient with unresectable tumour has shown partial response and the patient in high risk group has shown no recurrence.

Discussion

GIST are rare malignancies even though they are the most common sarcoma of the GIT. Majority of GIST occur in

Fig. 3. Small bowel GIST

middle age and older patients with mean reported age in different series varying between 58 and 60 years [8, 10, 11, 13]. However, in our study mean age was almost 10 years less than reported literature. Most of the studies have not shown a significant gender difference however in our study there was male preponderance [14]. Majority of GIST's are detected as incidental tumours however in our series most of the patients presented with palpable abdominal lump and pain (69.2%) [9, 10]. Obscure GI bleeding is a rare presentation and in our series we had a patient who was diagnosed to have GIST after an episode of GI bleed (Table 1).

Table 1 Comparison of historical data with our series

	Historical data	Our series
Age of presentation	Middle age (58–60 years)	46.2 years
Gender	No difference	Male common
Presentation	Bleeding 50% Pain 20%	Abdominal lump and pain 69%
Site	Stomach 60% Small bowel 30%	Stomach 31% Small bowel 54%
Location	Subserosal 30%	Subserosal 69%

Stomach and small intestine are common sites of origin of GIST, a small percentage occur in rectum, anus and elsewhere in abdominal cavity [4, 15]. In our case series 53.8% were of small intestine origin, 30.7% originated from the stomach. Sixty percent of GIST are submucosal

while 30% are subserosal, however in our series majority were subserosal 69.2% [11]. There are two principal histological patterns in GIST: spindle cell (60–70%) and epithelioid (30–40%). Combinations of the two are frequent [1, 16]. However in our series majority were of spindle cell type. Size, and mitotic index constitute a useful prognostic indicator for categorising these tumours into low and high risk groups (Table 2) [1].

Both the criteria of size and mitotic count need to be present for being classified into any one of the risk categories. Small bowel GIST have a higher propensity for malignant potential and a size of >5 cm and mitosis $\geq 2/50$ high power field are considered to be poor prognostic markers by some workers [17]. Irrespective of the risk group, all patients need to be on 6 monthly follow up with USG abdomen/CECT abdomen every 6 months for at least 5 years to detect early recurrences. All patients in our series who had small bowel GIST were >5 cm in size and none of them have had recurrences at mean follow up period of 1 year. Most common site for metastasis from malignant GIST are the liver and peritoneum, followed by lungs [7, 8, 11]. The liver accounts for nearly two thirds of metastatic lesions and the peritoneum about one-half to one-third. Presence of liver metastases is an adverse prognostic sign, however none of the patients in our series had liver metastases, including the patient who was found to be unresectable at surgery [1]. The overall 5-year survival rate in various studies has varied from 28% to 66% [11, 18, 19]. All the patients in this series are alive at 1 year (4–26 months) follow up. For GIST treated with surgery alone, recurrence rates at 5 years varies considerably, with recurrent disease developing in 2–15% of those with low risk and 70–90% of those with high risk primary tumours [20–22]. In the absence of adjuvant therapy, approximately 50% of patients receiving potentially curative surgery will develop either locally recurrent or metastatic disease within 5 years, yielding 5-year survival rates of 40–55% [11, 12]. Trials are presently on to assess whether this subset of patients requires adjuvant chemotherapy. In a significant change from NCCN 2007 guidelines, NCCN 2008 has now recommended adjuvant chemotherapy for all patients being categorised as intermediate, high risk groups and in incomplete resections/unresectable tumours [23, 24]. Newer drug like sunitinib a multiple tyrosine kinase inhibitor is indicated in imatinib-refractory disease.

Immunohistochemistry studies to determine CD117 positivity is required to prognosticate the response to postoperative adjuvant chemotherapy. In our study the same was not carried out for the first nine cases as it was not available in our institute. The last four cases were positive for CD117 and two of these were given adjuvant chemotherapy as per NCCN 2007 guidelines.

Table 2 Classification of primary GIST by risk of metastasis

Risk category	Very low risk	Low risk	Intermediate risk	High risk
Size	<2 cm	2–5 cm	<5 cm 5–10 cm	>10 cm Any size >5 cm
Mitotic count	<5/50 HPF	<5/50 HPF	6–10/50 HPF <5/50 HPF	Any mitotic rate >10/50 HPF >5/50 HPF

Conclusion

GIST are heterogenous group of tumours with varied presentation as shown by our study. All patients require accurate delineation by CECT scan and management has to be individualised. Immunohistochemistry should be done in all, and those who are in high risk, metastatic and unresectable groups require imatinib mesylate. Patients who are CD117 positive show good response to imatinib mesylate. Follow up is recommended with USG/CECT every 6 months.

References

- Fletcher CD, Berman JJ, Corless C, et al. (2002) Diagnosis of gastrointestinal tumour: A consensus approach. *Human Pathology* 33:459–465
- Perez-Atayde AR, Shamberger RC, Kozakewich HW (1993) Neuroectodermal differentiation of the gastrointestinal stromal tumours in the Carney triad. An ultrastructural and immunohistochemical study. *Am J Surg Path* 17:706–714
- Lauwers GY, ERLandson RA, Casper ES, Brennan MF, Woodruff JM (1993) Gastrointestinal autonomic nerve tumours. A clinicopathological, immunohistochemical, and ultrastructural study of 12 cases. *Am J Surg Path* 17:887–897
- Mukhopadhyay S, Dattagupta S (2002) Gastrointestinal stromal tumours: Bench-to-bedside review. In: *GI Surgery Annual*. Chattopadhyay TK (Ed.) 9:101–149
- Miettinen M, Sobin LH, Sarlomo-Rikala M (2002) Immunohistochemical spectrum of GIST at different sites and their differential diagnosis with a reference to CD117 (KIT). *Modern Pathology* 13:1134–1142
- Miettinen M (2002) New challenges in the identification of gastrointestinal stromal tumours and other possible KIT driven tumours. *Am J Clin Path* 117:183–185
- Berman J, O'Leary DJ (2001) Gastrointestinal stromal tumour workshop. *Human Pathology* 32:578–582
- Ludwig DJ, Traverso W (1997) Gut stromal tumours and their clinical behaviour. *Am J Surg* 173:390–394
- Hasegawa T, Matsuno Y, Shimoda T, Hirohashi S (2002) Gastrointestinal stromal tumour: Consistent CD117 immunostaining for diagnosis and prognostic classification based on tumour size and MIB-1 grade. *Human Pathology* 33:669–676
- Yao KA, Tala Monti MS, Langella RL, Shendler NM, Rao S, Small W Jr, et al. (2000) Primary gastrointestinal sarcomas: Analysis of prognostic factors and results of surgical management. *Surgery* 128:604–612
- DeMatteo RP, Lewis JL, Leung D, et al. (2000) Two hundred gastrointestinal stromal tumour: Recurrence patterns and prognostic factors for survival. *Ann Surg* 231:51–58
- Pierie JP, Choudry U, Muzikansky A, et al. (2001) The effect of surgery and grade on outcome of gastrointestinal stromal tumours. *Arch Surg* 136:383–389
- De Matteo RP, Heinrich MC, El-Rifai WM, Demetri G (2002) Clinical management of gastrointestinal stromal tumours: before and after STI-571. *Human Pathology* 33:466–477
- Miettinen M, Sarlomo-Rikala M, Lasota J (1998) Gastrointestinal stromal tumours. *Ann Chir Gynaecol* 87:278–281
- Miettinen M, Furlong M, Sarlomo-Rikala, Burke A, Sobin LH, Lasota J (2001) Gastrointestinal stromal tumours, intramural leiomyomas and leiomyosarcomas in the rectum and anus. A clinicopathologic, immunohistochemical and molecular genetic study of 144 cases. *Am J Surg Path* 25:1121–1133
- Graadt van Roggen JF, van Velthuysen MLF, Hogendoorn PCW (2001) The histopathological differential diagnosis of gastrointestinal stromal tumours. *J Clin Pathol* 54:96–103
- Brainard JA, Goldblum JR (1997) Stromal tumours of jejunum and ileum: A clinicopathological study of 39 cases. *Am J Surg Path* 21:407–416
- Adani GL, Marsello D, Sanna A, Mazzetti J, Anania G, Donini A (2002) Gastrointestinal stromal tumours: Evaluation of biological and clinical current opinions. *Chir Ital* 54: 127–131
- Ng EH, Pollock RE, Munsell MF, Atkinson EN, Romsdahl MM (1992) Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. *Ann Surg* 215:68–77
- Nilsson B, Bummig P, Meis-Kindblom JM, et al. (2005) Gastrointestinal stromal tumours: The incidence, prevalence, clinical course and prognostication in the pre-imatinib mesylate era. *Cancer* 103:821–829

21. Rossi CR, Mocellin S, Mencarelli R, et al. (2003) Gastrointestinal stromal tumours: From a surgical to a molecular approach. *Int J Cancer* 107:171–176
22. Demetri GD (2003) Identification and treatment of chemoresistant inoperable or metastatic GIST: Experience with the selective tyrosine kinase inhibitor imatinib mesylate (STI-571). *Eur J Cancer* 38:S52–S59
23. NCCN Practice Guidelines in Oncology (2007) Soft tissue sarcoma. Vol. 2
24. NCCN Practice Guidelines in Oncology (2008) Soft tissue sarcoma. Vol. 2