GASTROINTESTINAL STROMAL TUMOUR – REVISITED

Aparana Acharya, Anand Achayra

1. Assistant Professor. Department of General Surgery, Konaseema Institute of Medical Science and Research foundation, Amalapuram, Andhra Pradesh.
2. Associate Professor. Department of Pharmacology, Konaseema Institute of Medical Science and Research foundation, Amalapuram, Andhra Pradesh.

CORRESPONDING AUTHOR:
Dr. Mrs. A. M. Acharya,
Lecturer, Dept of Surgery,
Konaseema Inst of Medical Science and Research Foundation,
Amalapuram.
E-mail: draparnaacharya@gmail.com

ABSTRACT: Although less common than epithelial neoplasms, mesenchymal tumours of GI tract are not rare. The main bulk of these mesenchymal tumours is formed by Gastrointestinal stromal tumors (GIST). However they are not extensively documented, they are underestimated, poorly understood and inadequately treated for various reasons, particularly at peripheral centers in India. The gravity of the problem increases further as these tumours respond poorly to conventional cytotoxic chemotherapy and radiation therapy.
KEY WORDS – Gastro intestinal stromal tumour, GIST, c-kit

GIST is the commonest mesenchymal tumour of GI tract. It is also reported to arise from mesentery, omentum, retroperitoneum, and pelvis.[1]

Previously they were classified as smooth muscle tumours, nerve sheath tumours and tumours with no differentiation depending upon their morphologic features. The term stromal tumour was introduced in 1983, after Mazur and Clark failed to find ultrastructural evidence of smooth muscle or nerve sheath differentiation in several mesenchymal gastric tumours. GISTs are now thought to arise from stem cells related to interstitial cells of Cajal which are the pacemaker cells of the gut, associated with Auerbach's plexus.

Recent immunohistochemical and molecular evidence has prompted the concept of GIST as an umbrella term for all spindle cell tumours of the GI tract. A majority of GISTs (68–90%) express c-kit, a tyrosine kinase receptor of the immunoglobulin supergene family, which is also expressed by the gut pace maker cells – the interstitial cells of Cajal.[2]

So as to develop a consensus approach to the diagnosis and prognostication on the basis of morphologic features, GIST workshop held by NIH in April 2001 has recommended classification of GIST in very low risk, low risk, intermediate risk and high risk categories depending upon the size of tumour and mitotic count per 50 high power fields (Table I).[3] It has been modified to include the anatomic site by Rubin, Heinrich and Corless[1] because small bowel GISTs carry a higher risk of progression than gastric tumours of similar size and mitotic activity (Table II), although small intestinal GISTs are less common than gastric GISTs (36% and 51% respectively)[4] , they follow a more aggressive course. Markku Miettinen and others[5] analysed 906 cases of GIST arising from small intestine. They found 39% tumour related mortality, two times higher than gastric GISTs. Presence of diffuse nuclear atypia, epithelioid cytology, coagulative necrosis, ulceration and mucosal invasion were adverse prognostic factors while

small size, low mitotic activity and presence of skeinoid fibers were favorable prognostic factors.

The clinical symptoms depend upon the site of involvement, size of tumour and the precise portion of gut wall in which the tumour is located. The most common symptom is abdominal pain. GI bleeding, nausea, vomiting, weight loss and abdominal lump are other presenting symptoms. Clinical examination and imaging studies are contributory however a definite diagnosis is obtained only by histopathologic study. FNAC and endoscopic biopsy or frozen section may not be useful in distinguishing between benign and malignant GISTs.[3]

The aggressive GISTs commonly metastasize to the liver or throughout the abdomen. These tumours rarely metastasize to lymph nodes. Extra abdominal spread is mainly to the lungs and bone but is unusual except in most advanced cases.[1]

Mutations in exon 11 of the c-kit gene appear to be the central event in the pathogenesis of GIST (67% frequency), followed by exon 9 mutations (10% frequency), although mutations in exons 8, 13 and 17 may be detected less commonly.[1] These mutation have now become the central target for therapeutic intervention with the use of tyrosine kinase inhibitors although surgical management is the mainstay of therapy.

Routine lymph node resection is not recommended since GISTs only rarely metastasize to lymph nodes. [1] Use of tyrosine kinase inhibitors such as Imatinib mesylate and Sunitinib in adjuvant and neoadjuvant therapy has revolutionized the care of these patients, providing improved outcomes. With ongoing advancements in the field it is possible that targeted therapy may be selected in the future, based on the specific mutation exhibited in each GIST.[6]

CONCLUSION: Although GIST is the commonest mesenchymal tumour of GI tract, placing the tumour in proper prognostic category on morphologic grounds, immunohistochemical confirmation by c-kit expression studies is still not regularly done in peripheral centers of India due to various reasons like non-availability of immunohistochemical laboratory and most importantly unawareness on part of surgeons as well as pathologists . It is necessary to put the tumour in proper risk category, plan proper margin free surgical resection, give adjuvant therapy with tyrosine kinase inhibitors like Imatinib mesylate, for intermediate and high risk group tumours, tumours with advanced clinical stage and in presence of other high risk factors. Follow up of patient for Imatinib resistance and to see progression of the disease is necessary for need to switch over to alternative drugs like Sunitinib.

TABLE I[1] showing risk assessment unrelated to site of GIST

Risk	Size	Mitotic count (per 50 hpfs)
Very low risk	< 2 cm	< 5
Low risk	2 – 5 cm	< 5
Intermediate risk	< 5 cm 5 – 10 cm	6 – 10 < 5
High risk	> 5 cm > 10 cm Any size	> 5 Any mitotic rate > 10

TABLE II[7] showing risk Stratification of GIST related to the site

Risk category	Tumor size (cm)	Mitotic index (per 50 hpf)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1-5.0	≤5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10.0	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Non gastric
	5.1-10.0	≤5	Non gastric

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