

# Gastrointestinal stromal tumours (GIST)

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[Abstract](#)

[Keywords](#)

[Definition / diagnostic criteria](#)

[Incidence / frequency](#)

[Clinical description](#)

[Pathological features](#)

[Etiology / histogenesis](#)

[Differential diagnosis](#)

[Disease progression and prognostic factors](#)

[Diagnostic methods](#)

[Treatment](#)

[Unresolved questions](#)

[References](#)

## Abstract

*Gastrointestinal stromal tumours (GISTs) are defined as gastrointestinal mesenchymal tumours expressing a protooncogene protein called CD117 detected by immunohistochemistry. GISTs are rare and constitute about 1-3% of all gastrointestinal (GI) malignancies, nevertheless they are the commonest type of GI mesenchymal tumours. Data concerning the worldwide prevalence of GISTs are lacking. Data from population based studies in Finland suggested annual incidence of all GISTs around 10-20 per million. Annual incidence of 6.8 cases per million and 14.5 per million population was estimated in USA and in western Sweden population, respectively, with slight predominance among men. GISTs differ from gastrointestinal smooth muscle and neural tumours. Clinical features depend on the size and site of the tumour and include acute or chronic bleeding, intestinal obstruction, perforation, alteration of bowel habits, vague abdominal discomfort, dysphagia and externally palpable abdominal mass. It is now believed that GISTs originate from gastrointestinal pacemaker cells known as interstitial cells of Cajal, that control gut motility or from a precursor of these cells. Many GISTs contain mutations mostly in exon 11 and to a lesser extent in exons 9, 13 or 17 of the c-kit (KIT) protooncogene coding for c-KIT (CD117). Some GISTs have mutation of the platelet-derived growth factor receptor-alpha (PDGFRA) gene. Complete surgical excision is the treatment of choice for localised GISTs. The role of radiotherapy is limited by the potential toxicity to surrounding structures. Finding the antitumour effects of the molecular inhibitor imatinib mesylate (Glivec<sup>TM</sup>, Novartis, Basel, Switzerland) in metastatic and inoperable GISTs has been a remarkable breakthrough. To implement therapy it is important to diagnose GISTs accurately and distinguish them from other gastrointestinal mesenchymal tumours.*

## Keywords

gastrointestinal mesenchymal tumours, CD117, c-KIT gene, PDGRA gene, imatinib mesylate

## Definition / diagnostic criteria

Gastrointestinal stromal tumours (GISTs) are defined as gastrointestinal mesenchymal tumours expressing a protooncogene protein

called CD117 detected by immunohistochemistry (1,2). They are different from gastrointestinal smooth muscle tumours (leiomyoma and leiomyosarcoma) and neural tumours

(schwannoma). Tumours previously described as gastrointestinal autonomic nerve tumour (GANT) are now regarded as variants of GIST (3,4).

### Incidence / frequency

Data from population based studies in Finland suggest that the annual incidence of all GISTs is around 10-20/ million and that of malignant GISTs is about 4 cases per million of population (5,6). Annual incidence of 6.8 cases per 1,000,000 population was estimated in USA (51% of cases were in the stomach, 36% small intestine, 7% colon, 5% rectum, and 1% in the esophagus), with slight predominance among men and among Blacks (31). The annual incidence of GISTs was 14.5 per million in western Sweden population (32). The true incidence may be higher because of under-diagnosis in the past, and the reporting of some tumours as smooth muscle tumours or as sarcomas of uncertain histogenesis (1). A large majority of tumours previously diagnosed as smooth muscle tumours of the gastrointestinal tract are probably GISTs (1). GISTs are now known to constitute the majority of all gastrointestinal mesenchymal tumours.

### Clinical description

GISTs usually affect middle-aged and older patients with a median age of 50-60 years (4). They are rare before the age of 40-years and very rare in children (5). About 60-70% of GISTs occur in the stomach, 20-30% in the small intestine and 10% or less in the oesophagus, colon and rectum (1). Tumours with similar features (designated as extragastrointestinal stromal tumours, EGIST) may arise in the mesentery, omentum and retroperitoneum (7). The clinical presentation depends on the size and site of the tumour. Small asymptomatic GISTs, usually less than 2cm in diameter, are detected incidentally at laparotomy or in specimens that have been resected for other conditions, and at endoscopy, usually in the gastric submucosa (5). Larger tumours present with vague abdominal discomfort (4), acute or chronic gastrointestinal haemorrhage, dysphagia (8), intestinal obstruction, perforation or altered bowel habit (5). Very large GISTs presenting as externally palpable intra-abdominal masses, are likely to be malignant (4). Some patients may present with liver metastases.

### Pathological features

GISTs are usually unencapsulated but well circumscribed masses. The cut surface has a whorled fibroid-like or a softer more fleshy appearance. Larger lesions show cystic

degeneration or central necrosis. Ulceration of the overlying mucosa is common. The predominant histologic pattern, seen in 70-80% of GISTs, is of a spindle cell tumour with a fascicular or storiform growth pattern (1,9). About 20-30% of tumours are predominantly composed of large round or polygonal epithelioid cells with abundant often eosinophilic or clear cytoplasm (1,4,9). Mixed spindle and epithelioid tumours are common. Small intestinal GISTs may contain eosinophilic, hyaline, PAS positive diastase resistant, extracellular globules or more elongated collagen known as skeinoid fibres (10).

Expression of CD117 is seen in 95 % of GISTs regardless of the site of origin, histologic appearance and biologic behaviour (1,9). Approximately 60-80% of GISTs express CD34 (5,9).

### Etiology / histogenesis

The immunophenotypic (CD117 positive) and ultrastructural resemblance of GISTs to the interstitial cells of Cajal, gastrointestinal pacemaker cells which control gut motility, suggests a histogenesis from the latter cells (11). CD117, the c-KIT proto-oncogene protein is a transmembrane receptor for a growth factor known as stem cell factor (SCF) or mast cell growth factor. It is encoded by the *c-KIT* proto-oncogene located on chromosome 4q11-21 (12). It has extracellular, intramembranous and intracellular domains. Binding of SCF ligand to the receptor leads to dimerization of the receptor. This activates tyrosine kinase located in the intracellular domain, leading to activation of further intracellular signalling cascades controlling cell proliferation, adhesion and differentiation.

Mutations in the *c-KIT* gene have been identified in many sporadic and familial cases of GISTs. They are present in approximately 80-85% of GISTs, most commonly in exon 11 which encodes the juxta-membrane domain. These mutations result in gain of function with permanent activation of the receptor, in the absence of binding of the stem cell factor ligand (13,14,15). Less commonly mutations involve exons 9, 13 or 17 which encode the extracellular and kinase domains respectively (13,16). The *c-KIT* mutations which alter the enzymatic portion of the KIT protein are called enzymatic mutations, while those that involve the regulatory portion are called regulatory-type mutations (13). *In vitro* studies suggest that GISTs with regulatory-region *KIT* mutations are more likely to respond to ST1-571 than GISTs with enzymatic-region mutations (13). The *c-KIT* mutations probably occur as early events in the

process of development of GISTs. Such mutations have been demonstrated in GISTs measuring one centimetre or less in diameter (17). Uncommonly, GISTs develop in families with germline mutations of *c-KIT* in exons 11 and 13 (13).

A variety of chromosomal abnormalities have been described in GISTs (18), most typically monosomy of chromosomes 14 and 22 and deletions of 1p (18,19,20). Malignant GISTs often show additional abnormalities including amplification of 8q and 17q (21). These cytogenetic aberrations are undoubtedly important in the pathogenesis of GIST but are currently not used as diagnostic adjuncts.

Recently, some GISTs without the *KIT* mutation have been found to express a mutation in another tyrosine kinase receptor gene, the *PDGRA* gene (platelet-derived growth factor receptor- $\alpha$ ) (33). *PDGRA* mutations were found to occur in either exon 18 or 12, as found in a series of 322 GISTs (34). The same study showed that 12% of GISTs were wild type for both *KIT* and *PDGFRA*.

#### Differential diagnosis

GISTs has to be distinguished from true smooth muscle tumours and schwannomas of the gastrointestinal tract (1). The differential diagnosis include intra-abdominal fibromatosis, inflammatory fibroid polyps, paragangliomas and metastatic malignant melanoma (1). Histological and immunohistochemical features will help to distinguish GISTs from these entities (1).

#### Disease progression and prognostic factors

GISTs spread to the liver and within the abdominal cavity (22). Bone and lung metastases as well as lymph node metastases are rare (5). Soft tissue metastases may occur in the internal aspect of the abdominal wall or the subcutaneous tissue (5).

Tumours in the small intestine are known to behave most aggressively than those in the stomach (6,23,24). Metastasis at the time of presentation (24) and peritoneal seeding at the time of the primary operation (25,26) are associated with a very poor prognosis. Although large, mitotically active tumours, with necrosis, predictably behave aggressively, even small cytologically bland and poorly mitotic tumours may occasionally metastasize (6,25). As it is difficult to predict the malignant potential of GISTs based on clinicopathological features, it is more appropriate to divide them into low, intermediate and high-risk categories based on an estimation of their potential for recurrence and metastases. Figure 1 shows an algorithm based on the consensus approach for assessing

the risk of malignancy reached at a National Institutes of Health workshop held in April 2001 (9). As a small subset of GISTs behave in an unpredictable manner, no tumour can be labelled as unequivocally benign (9). Thus all patients with GIST should be carefully followed up for an indefinite period.

#### Diagnostic methods

Confirmation of diagnosis requires a biopsy with demonstration of CD117 positivity in tumour cells. CD117-negative cases require tests for mutations of *c-KIT* and *PDGFRA*. Computing tomography (CT) and Magnetic resonance imaging (MRI) scans will help to determine extent and spread of disease.

PTEN (phosphatase and tensin homologue deleted on chromosome 10) downregulation is implied in GIST progression. The immunohistochemical assessment of PTEN status appears to be a promising method of GIST prognostication (35).

#### Treatment

Complete surgical excision is the treatment of choice for localised GISTs. The role of radiotherapy is limited by the potential toxicity to surrounding structures, especially the intestines (27). There has been a 40-69% partial response of inoperable and metastatic GISTs to targeted therapy using imatinib mesylate {Glivec, Novartis} (27,28). This is a major breakthrough because GISTs were previously regarded as being generally resistant to conventional chemotherapy (27). Imatinib mesylate (Glivec) is a synthetic tyrosine kinase inhibitor, which has an established role in the management of interferon resistant chronic myeloid leukaemia (29). It was initially shown to have striking antitumour effect in a single Finnish patient with metastatic GIST (29). Larger trials in America and in Europe have confirmed this finding (27,28,30). Imatinib is now considered to be the drug of choice for metastatic and inoperable GISTs (27,28).

#### Unresolved questions

There remains a small problematic group of tumours with morphological features of GISTs without expression of CD117 (5). Some pathologists designate these as GIST-like tumours, but the exact nature of these tumours will have to be defined in the future.

Some GISTs that lack *c-KIT* mutations have high *KIT* kinase activity. Such GISTs might contain *KIT* mutations which are not readily detected by conventional screening methods or activation might be due to nonmutational mechanisms (13).

These mechanisms will have to be resolved in the future.

Another problem is resistance to imatinib mesylate, whether primary (5-12 % of cases) or secondary. The latter type is observed in about 40% of patients after 2 years of treatment. Additional targeted therapies are currently tested.

## References

1. De Silva CM, Reid R. Gastrointestinal stromal tumours (GIST): C-kit mutations, CD117 expression, differential diagnosis and targeted cancer therapy with imatinib. *Pathol Oncol Res.* 2003; 9:13-19.
2. Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, Miettinen M. CD117: a sensitive marker for gastrointestinal stromal tumours that is more specific than CD34. *Mod Pathol* 1998; 11:728-734.
3. Lee JR, Joshi V, Griffin JW Jr, Lasota J, Miettinen M. Gastrointestinal autonomic nerve tumor: immunohistochemical and molecular identity with gastrointestinal stromal tumor. *Am J Surg Pathol* 2001; 25:979-987.
4. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999; 30:1213-1220.
5. Miettinen M, Lasota J. Gastrointestinal stromal tumors-definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001; 438:1-12.
6. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumours. *Annales Chirurgiae et Gynaecologiae* 1998; 87:278-281.
7. Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastric (soft tissue) stromal tumours: an analysis of 48 cases with emphasis on histological predictors of outcome. *Mod Pathol* 2000; 13: 577-585.
8. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. *Am J Surg Pathol* 2000; 24:211-222.
9. Fletcher CDM, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002; 33:459-465.
10. Ming KW. Small intestinal stromal tumors with skeinoid fibers. Clinicopathological, immunohistochemical and ultrastructural investigations. *Am J Surg Pathol* 1992; 16:145-155.
11. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol* 1998; 152:1259-1269.
12. Vliagoftis H, Worobec AS, Metcalfe DD. The proto-oncogene c-kit and c-kit ligand in human disease. *J Allerg Clin Immunol* 1997; 100:435-440.
13. Heinrich MC, Rubin BP, Longley BJ, Fletcher JA. Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. *Human Pathol* 2002; 33:484-495.
14. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; 279:577-580.
15. Nakahara M, Isozaki K, Hirota S, Miyagawa J, Hase-Sawada N, Taniguchi M, et al. A novel gain-of-function mutation of c-kit gene in gastrointestinal stromal tumors. *Gastroenterology* 1998; 115:1090-1095.
16. Lux ML, Rubin BP, Biase TL, Chen CJ, Maclure T, Demetri G, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol* 2000; 156:791-795.
17. Corless CL, McGreeney L, Haley A, Town A, Heinrich MC. KIT mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. *Am J Pathol* 2002; 160:1567-1572.
18. Andersson J, Sjogren H, Meis-Kindblom JM, Stenman G, Aman P, Kindblom LG. The complexity of KIT gene mutations and chromosome rearrangements and their clinical correlation in gastrointestinal stromal (pacemaker cell) tumors. *Am J Pathol* 2002; 160:15-22.
19. El-Rifai W, Sarlomo-Rikala M, Miettinen M, Knuutila S, Andersson LCA. DNA copy number losses in chromosome 14: an early change in gastrointestinal stromal tumours. *Cancer Res* 1996; 56:3230-3233.
20. Sarlomo-Rikala M, El-Rifai W, Andersson LC, Miettinen M, Knuutila S. Different patterns of DNA copy changes in gastrointestinal stromal tumors, leiomyomas and schwannomas. *Hum Pathol* 1998; 29:476-481.
21. Debiec-Rychter M, Lasota J, Sarlomo-Rikala M, Kordek R, Miettinen M. Chromosomal aberrations in malignant gastrointestinal tumors correlation with c-KIT gene mutation. *Cancer Genet Cytogenet* 2001; 128:24-30.
22. Franquemont DW. Differentiation and risk assessment of gastrointestinal stromal tumors. *Am J Clin Pathol* 1995; 103:41-47.

23. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth muscle (stromal) tumors: dependence on anatomic site. *Am J Surg Pathol* 1999; 23:82-87.
24. Miettinen M, El-Rifai W, Sobin LH, Lasota J. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. *Hum Pathol* 2002; 33:478-483.
25. Cooper PN, Quirke P, Hardy GJ, Dixon MF. A flow cytometric, clinical and histologic study of stromal neoplasms of the gastrointestinal tract. *Am J Surg Pathol* 1992; 16:163-170.
26. Cunningham RE, Federspiel BH, McCarthy WF, Sobin LH, O'Leary TJ. Predicting prognosis of gastrointestinal smooth muscle tumors. Role of clinical and histologic evaluation, flow cytometry, and image cytometry. *Am J Surg Pathol* 1993; 17: 588-594.
27. Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. *Human Pathol* 2002; 33:466-477.
28. Heinrich MC, Blanke CD, Druker BJ, Corless CL. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. *J Clin Oncol* 2002; 20:1692-1703.
29. Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, et al. Effect of tyrosine kinase inhibitor STI-571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; 344:1052-1056
30. Van Oosterom AT, Judson I, Verweij J, Stroobants S, di Paola ED, Dimitrijevic S et al. Safety and efficacy of imatinib (STI-571) in metastatic gastrointestinal stromal tumors: A phase 1 study. *Lancet* 2001; 358:1421-1423.
31. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol.* 2005; 100:162-8.
32. Nilsson B, Bummig P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: The incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. *Cancer.* 2005 Jan 12; [Epub ahead of print]
33. Tamborini E, Bonadiman L, Greco A, et al: A new mutation in the KIT ATP pocket causes acquired resistance to imatinib in a gastrointestinal stromal tumor patient. *Gastroenterology* 2004 Jul; 127(1): 294-9
34. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol.* 2004 Sep 15;22(18):3813-25.
35. Ricci R, Maggiano N, Castri F, Rinelli A, Murazio M, Pacelli F, Potenza AE, Vecchio FM, Larocca LM. Role of PTEN in gastrointestinal stromal tumor progression. *Arch Pathol Lab Med.* 2004 Apr;128(4):421-5.

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**Figure 1**

Algorithm based on the consensus approach for assessing the risk of malignancy of GIST reached at a National Institutes of Health workshop held in April 2001 (9).

