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Current perspectives on the epidemiology of gastrointestinal stromal tumours

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Abstract

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal malignancies of the gastrointestinal (GI) tract that are a distinct disease entity based on their molecular pathogenesis, immunohistochemical staining, and responsiveness to targeted therapy. The annual incidence of GIST is 11 to 15 cases per million in studies based on Caucasian populations, with GISTs detected at autopsy and those with a low malignancy potential included. GISTs vary in malignant potential ranging from small, incidentally detected tumours with excellent outcome, to aggressive sarcomas. The appearance and behaviour of GISTs can differ depending on the location within regions of the GI tract. Approximately one third of GISTs worldwide are in the high-risk category for malignant potential, and an inverse correlation between level of risk and survival of GIST patients has been observed. *KIT*, or more rarely *PDGFRA*, gene mutations are key to GIST oncogenesis. Criteria for identification of GIST, based on immunoreactivity for the CD117 epitope expressed on KIT, have improved the accuracy of GIST diagnosis and contributed to recognition of GIST as a distinct disease entity. Other markers for diagnostic specificity for GIST are under consideration. Improved diagnosis has led to a slight increase in the observed incidence rate of GIST, which has stabilised in recent years. GISTs are refractory to conventional chemotherapy and surgery was the most effective therapy for GIST prior to the development of the targeted therapy imatinib. Although surgery remains first-line therapy for primary GIST, imatinib is indicated as frontline therapy for metastatic or unresectable GIST.

Keywords: Gastrointestinal stromal tumour; KIT; PDGFR; Imatinib mesylate; Tyrosine kinase inhibitors

1. Incidence and prevalence of GIST

Gastrointestinal stromal tumours (GISTs) are rare, comprising approximately 1% of all gastrointestinal (GI) cancers. The epidemiology of GISTs is still incompletely known, in part because GIST is a novel disease entity. These tumours were often classified as GI leiomyomas, leiomyosarcomas or leiomyoblastomas as recently as the year 2000 [1,2], but are now considered a disease entity distinct from leiomyosarcoma due to important differences in clinical features, molecular pathogenesis, and responsiveness to cancer therapy. GISTs also vary greatly in size, morphology, and malignancy potential, creating a continuum of neoplasms with uncertain malignancy potential ranging from virtually benign tumours to overtly malignant, aggressive cancers. The more indolent GISTs are typically small, sometimes incidentally found tumours that might not have surfaced during the lifetime of a patient, whereas other GISTs may present with overt metastases already at the time of the diagnosis.

Three recent Northern European population based studies, using up-to-date diagnostic criteria, placed the annual incidence of GIST at 14.5 per million in Sweden, 11 per million in Iceland, and 12.7 per million in The Netherlands [1–3]. In these series [1,3], approximately 10% of cases were detected at autopsy and approximately 20% of incidental cases were detected at endoscopy or imaging of the abdomen, or at surgery for other conditions. In line with these findings, a study from southern Finland reported an estimated annual incidence of 10 to 20 per million of the population [4].

The proportion of overtly malignant or high-risk GISTs is considered to be 20–45% of all GISTs [1,4], which suggests that the annual incidence of GISTs with a high malignancy potential is about 5 per million. This figure is approximately similar to the one reported in a recent study, which used the Surveillance, Epidemiology, and End Results (SEER) registry from the National Cancer Institute to identify all cases of GIST diagnosed in the USA from 1992 to 2000. This study found the age-adjusted yearly incidence of GIST to be 6.8 per million [5]. The incidence of GIST may need to be revised somewhat upward worldwide in the future [2]. A population-based study from southwestern Sweden reported the prevalence of GIST as 129 per million, and the prevalence of GISTs considered to be either overtly

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1359-6349/ $ – see front matter

malignant or to have a high risk for recurrence at 31 per million [1].

Despite this overall rare occurrence, GISTs are the most frequently encountered soft-tissue sarcoma of the GI tract. As the annual incidence of all soft-tissue sarcomas is approximately 30 per million [6,7], GISTs might constitute approximately one sixth to one third of all soft-tissue sarcomas depending on whether there is an accounting for small and incidental GISTs. Even this broad estimate should be viewed with caution, as few epidemiological data are available from non-Caucasian populations, the diagnostic criteria for GIST have continued to evolve with time, and many small, asymptomatic GISTs may remain undetected. In one study, 2 GISTs were found per 1000 autopsies performed [1], suggesting that asymptomatic GISTs of low malignancy potential may not be uncommon tumours in the elderly general population, and that these GISTs might be much more frequent than GISTs with a high malignancy potential. In the SEER data, the incidence rate was higher among blacks [5].

2. Clinical presentation

The median age of adults at diagnosis of GIST is 66 to 69 years in population-based studies, but these series include tumours detected incidentally or at autopsy [1,3]. Such GISTs are diagnosed approximately one decade later than symptomatic GISTs, at the median age of approximately 75 years. In a large series consisting of 1765 gastric GISTs from the Armed Forces Institute of Pathology (AFIP), Washington, DC, the median age at diagnosis was 63 years [8]. Similarly, in the US SEER registry data from 1992 to 2000 (n = 1445), the median age at the time of diagnosis was 63 years. In both the AFIP and the SEER series, 54% to 55% of GISTs occurred in males, whereas an equal gender distribution was found in a population-based analysis from Sweden as well as from Korea [1,9]. Only about 3% of GISTs are diagnosed before the age of 21 years [8], and GISTs arise only exceptionally in children [1,3,10]. A recent case report described a 3-cm caecal GIST that caused symptoms of bowel obstruction in a newborn infant [11]. The rare paediatric GISTs seem to have specific features; they occur often in girls, are located in the stomach, have the epithelioid type tissue morphology, have a protracted clinical course, and lack or have unusual *KIT* and *PDGFRA* gene mutations [12,13].

The most common symptom of GIST at presentation is bleeding [8]. GISTs typically grow between the bowel loops and the abdominal organs ("endophytically"), but they may also erode the GI tract lumen. Thus, bleeding may take place either into the abdominal cavity – usually causing acute abdominal pain and severe anaemia – or into the stomach or the intestine – causing haematemesis, melena, and anaemia. Patients with GIST may also exhibit various other symptoms that include early satiety, bloating, abdominal pain or discomfort, obstructive jaundice, dysphagia, fever, and anaemia-related symptoms such as fatigue and palpitations [8].

Table 1
Location of primary GIST tumours[a]

Site	Incidence (%)
Oesophagus	<5
Stomach	39–60
Small bowel	30–42
Colon–rectum	5–11
Other–unknown (omentum, mesentery, peritoneum, retroperitoneum)	5–7

[a] Adapted from refs. [14,15].

GISTs can originate anywhere in the GI tract, from the lower oesophagus to the anus; however, the stomach (39–60%) and small intestine (30–42%) are the most common locations for these tumours [4,14–16]. The colon, rectum, and appendix (together 5–11%), oesophagus, mesentery, retroperitoneum, and other intra-abdominal organs are unusual sites of GIST (Table 1). In the SEER data, 51% of the cases arose from the stomach, 36% from the small intestine, 7% from the colon, 5% from the rectum, and 1% from the oesophagus [5]. A recent multi-institutional survey of the approximate incidence and clinicopathologic and immunohistochemical features of GIST in Korea suggests that there are only minor differences in the demographic features and immunohistochemistry staining results between the Korean and Western populations [9].

A peculiar feature of GISTs is that they often give rise to numerous intra-abdominal metastases located on the peritoneal, omental, mesenteric, and other serosal surfaces. They frequently give rise to liver metastases, whereas extra-abdominal metastases are rare. Even in the late phases of advanced disease, macroscopic extra-abdominal metastases are often few or absent, resulting in a characteristic clinical presentation with a greatly enlarged abdomen coupled with muscle wasting. GISTs have a high tendency to seed, and the intra-abdominal lesions probably result from tumour cell seeding into the abdominal cavity, whereas liver metastases probably result from haematogenous spread of GIST cells into the liver. GIST patients may have metastases in abdominal surgical scars and sometimes even in needle tracts, findings which are compatible with the high tendency of the tumour to seed. Lymph node metastases are rare.

3. Outcome and prognostic features

GISTs range in size from 0.5 cm to 35 cm, with a median size between 4.6 cm and 7 cm [1,3]. GIST size and cell proliferation rate, usually assessed by counting the mitotic rate, are considered to be key prognostic indicators for malignant behaviour of GISTs (Table 2) [17]. Tumours that are small (<2 cm) and show mitotic activity not exceeding

Table 2
Assessment of the risk of recurrence in resectable GIST[a]

Risk	Size (cm)	Mitotic count/50 HPFs[b]
Very low	<2	<5
Low	2–5	<5
Intermediate	<5	6–10
	5–10	<5
High	>10	Any mitotic rate
	Any	>10
	>5	>5

[a] Adapted from ref. [17].
[b] HPF, high power field.

5 mitoses per 50 high-power fields (HPFs) have an excellent prognosis, probably independent of site, although this has not been shown specifically for all sites. Tumours with a high mitotic rate (>5/50 HPFs) tend to result in a poorer prognosis [18]. In several studies gastric GISTs exhibit a lower tumour-associated mortality rate compared with GISTs originating elsewhere. Tumour volume and negative margins after surgical resection have been shown to be good prognostic factors in GIST, whereas sex of GIST patients, tumour histological type (spindle cell, epithelioid, or mixed), or KIT and CD34 immunoreactivity do not seem to be significant independent prognostic indicators [1,5,19]. GISTs that have metastasised to the liver at presentation or have recurred within the peritoneum have a poor prognosis.

A consensus approach for defining the risk of aggressive behaviour in GISTs, based on tumour size and mitotic count, has been proposed [17]. In a population-based study examining survival rates with GIST, use of these consensus prognostic classification criteria to stratify GIST patients into high-, medium- and low-risk groups resulted in an inverse correlation between the level of risk and survival [1]. Unexpectedly, patients with an intermediate risk of recurrence had favourable outcome in this particular series, and a few of those diagnosed with an overtly malignant GIST (with metastases present at the time of the diagnosis) survived over 10 years following the diagnosis (Fig. 1).

Most GISTs respond poorly to conventional chemotherapy. The impact of radiation therapy in the treatment of GISTs is limited and the responsiveness of GISTs to radiation therapy is not well known [20,21]. Surgery is currently the first-line treatment for primary resectable GIST. However, even after complete resection of localised primary tumour, the 5-year survival rate for patients with GIST ranges from 50% to 65% [20,22–24]. The relative 5-year survival rate for GIST patients diagnosed in the USA from 1992 to 2000 was 45% [5]. Ten percent to 25% of GIST patients present with metastatic disease [1,5], and between 40% and 90% of all GIST surgical patients have a postoperative recurrence or metastasis [16]. Outcomes in patients with metastatic GIST or recurrence after primary

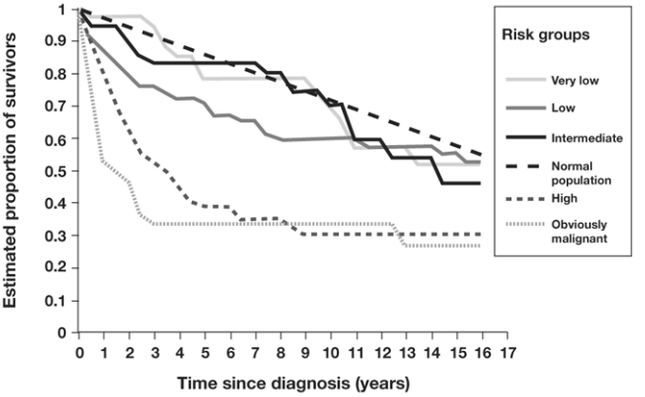

Fig. 1. Estimated overall survival of patients with clinically diagnosed GIST compared as a function of risk group. Comparison is made with an age-matched and gender-matched general population.

resection are poor. The median survival duration for patients with metastatic GIST or with local recurrence was 10 to 20 months before the imatinib era [20,22–24], although a small number of patients with intra-abdominal metastasis survive up to 20 years [8].

4. Histopathology of GIST

GISTs probably originate from interstitial cells of Cajal (ICCs) or their precursors [25,26] ICCs are the pacemaker cells of the GI tract controlling gut motility. Macroscopically, GISTs are usually well circumscribed and surrounded by a pseudocapsule. Morphologically, GISTs are a heterogeneous group of neoplasms that may vary in composition within and between different tumours. GIST cell morphology is usually spindle-shaped (70%); some GISTs have rounded cells (the epithelioid type, 20%) or a mixture, but can also be pleomorphic [17]. The appearance and clinical behaviour of GISTs can vary in different portions of the GI tract. Large GIST lesions often show cystic degeneration or central necrosis [27].

Studies have identified a key diagnostic marker for GIST using antibodies to the CD117 epitope present on KIT, a receptor tyrosine kinase for the stem cell factor (SCF) [17,28,29]. Approximately 90–95% of GISTs are immunohistochemically positive for KIT protein expression, exhibiting a diffuse, focal, or mixed staining pattern [1,4]. Detectable KIT expression, judged together with immunohistochemical stainings for other proteins and with tumour morphology, is very useful in distinguishing GISTs from other mesenchymal neoplasms such as leiomyomas, leiomyosarcomas, schwannomas, and neurofibromas. KIT immunoreactivity does not, however, correlate with overall survival.

Other markers recently identified may also have diagnostic specificity for GIST. For example, 98% of GISTs express DOG1 [30], a transmembrane protein of unknown function rarely expressed in other soft-tissue tumours, leading to the suggestion that the DOG1 marker might be useful in GIST

diagnosis provided that this method of detection is available. In addition, an isoform of protein kinase C, PKC θ, has been found to be highly expressed and constitutively phosphorylated in GIST [31–33]. PKC θ may serve as a diagnostic marker for GIST, and this marker may be particularly useful for identifying GISTs negative for KIT expression [33]. Most GISTs have also been shown to stain positively for ras p21, one of the downstream mediators of KIT signalling [34].

5. Molecular analysis of GIST

Constitutively activating mutations of *KIT* are central to GIST oncogenesis, resulting in increased cell proliferation and enhanced cell survival [25,35]. In one series consisting of 322 GISTs, mutations in exon 11 of the gene encoding KIT were the most common GIST-associated mutations (66.9%), whereas 9.8% of GISTs had *KIT* exon 9 mutations, 1.3% had *KIT* exon 13 mutations, and 0.6% had *KIT* exon 17 mutations [36]. In an analysis of 1105 GIST lesions, 7.2% expressed constitutively activating mutations in the gene encoding platelet-derived growth factor receptor α (PDGFRα), a receptor tyrosine kinase closely related to KIT [37–39]. In this study, among the 80 GISTs with mutated *PDGFRA*, 66 of the mutations occurred in exon 18, 11 were in exon 12, and 3 were in exon 14. Germline mutations in *KIT* or *PDGFRA* have also been detected in familial GIST [40,41]. *KIT* and *PDGFRA* mutations seem to be alternative, and mutually exclusive, oncogenic pathways for GIST [42]. The remainder of GISTs, approximately 12%, is wild type for both *KIT* and *PDGFRA*. Patients with neurofibromatosis-associated GIST usually do not have *KIT* mutations, but the tumours may sometimes have mutated *NF1* [43]. Similarly, GISTs occurring in patients with the Carney's triad do not harbour *KIT* or *PDGFRA* mutations. Carney's triad is a very rare syndrome of unknown cause primarily affecting young women and consisting of gastric GISTs, extra-adrenal paraganglioma, and pulmonary chondroma.

6. Imatinib

Understanding the molecular pathophysiology of GIST led to the clinical development of imatinib for treating patients with this disease. Imatinib is an orally administered 2-phenylaminopyrimidine derivative that acts as a competitive inhibitor of the adenosine triphosphate (ATP) binding domain of KIT, PDGFRα, and certain other tyrosine kinases [44–48]. Imatinib inhibits dysregulated KIT or PDGFRα kinase activity, preventing receptor autophosphorylation and subsequent downstream signalling. In preclinical studies, imatinib decreased cell proliferation and increased early apoptosis in a dose-dependent manner [46, 49,50].

Imatinib therapy for advanced GIST has highlighted the concept of molecularly targeted therapy and represents the first effective systemic therapy for patients with metastatic or unresectable GIST. A subsequent article in this supplement, *Molecular basis for treatment of gastrointestinal stromal tumours* by Michael Heinrich, elaborates the clinical evidence in support of the first-line indication of imatinib for metastatic and unresectable GIST as well as the molecular basis for responses to imatinib. The last article in this supplement, *Optimising therapy for GIST patients* by Peter Reichardt, discusses practical clinical strategies to optimise imatinib therapy for GIST.

A summary of the clinical data indicates that imatinib stabilises GIST and induces objective responses, thereby providing clinical benefit in the majority of advanced GIST patients [51–55]. GISTs with *KIT* mutations in exon 11 (juxtamembrane domain) have the best response to imatinib followed by GISTs with exon 9 (extracellular domain) mutations. Clinical responses have been observed in some GISTs expressing exon 13 and exon 17 mutations of *KIT* or GISTs expressing exon 12 mutations of *PDGFRA* [37,39], and some *PDGFRA* exon 18 and 14 mutations show sensitivity to imatinib *in vitro* [37].

7. Conclusions

GISTs are rare, but potentially lethal, neoplasms with a highly variable malignancy potential. GISTs have undergone dramatic diagnostic and therapeutic reconsideration because of molecular advances in basic science and drug development. A majority of GISTs express the CD117 antigen (KIT), which is useful in distinguishing GIST from other tumours in the differential diagnosis, but other proteins, such as PKC θ, may complement CD117 – especially in the diagnosis of GISTs expressing undetectable levels of KIT. Improved diagnostic criteria for GIST have led to recent modest increases in GIST incidence over the last several years, but since the advent of these developments the incidence of diagnosed GIST seems to have stabilised [2]. Emerging data indicate that epidemiological characteristics of GIST may be relatively uniform worldwide. The realisation that GIST molecular pathogenesis is linked with activating mutations of *KIT*, or occasionally *PDGFRA*, has led to improved understanding of these tumours and paved the way for development of effective targeted systemic therapy.

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