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Gastrointestinal Stromal Tumours: A Contemporary Review on Pathogenesis, Morphology and Prognosis

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1. Introduction

Gastrointestinal stromal tumours (GISTs) comprise the largest subset of mesenchymal tumours of the digestive tract. Over the past 10 years, this group of tumours has emerged from a poorly understood neoplasm to a well defined tumour entity.

The first accurate description of mesenchymal neoplasms of the gastrointestinal tract was in 1941 (Golden T & Stout AP, 1941). Traditionally, these tumours were thought to be derived from smooth muscle cells, based on their resemblance to smooth muscle tumours. They were referred to as leiomyomas, bizarre leiomyomas (Stout AP, 1976), cellular leiomyomas (Appelman, 1977) and leiomyosarcomas. However, the advent of electron microscopy revealed that only a few of them have convincing ultrastructural evidence of smooth muscle differentiation. In addition, the application of immunohistochemistry clearly demonstrated that many of these tumours lack the features of smooth muscle differentiation. This led Mazur and Clark in 1983 to introduce the generic designation "stromal tumour" (Mazur & Clark, 1983).

A little later, in 1984, Herrera et al (Herrera et al., 1984) introduced the concept of "plexosarcoma" to acknowledge the existence of a small subset of stromal tumours with autonomic neuronal differentiation which became better known as gastrointestinal autonomic nerve tumours (GANTs) (Lauwers et al., 1993).

A considerable controversy arose as to the line of differentiation these tumours take. Some tumours exhibit a myogenic phenotype, while others may show a neural differentiation, mixed or no differentiation at all, the so called "null phenotype". Some enthusiasm was generated by the recognition that a significant proportion of stromal tumours express CD34 (Miettinen et al., 1995). However the diagnostic utility of this marker was hampered by its poor specificity. As a consequence of the lack of reproducible diagnostic criteria, GIST represented a generic term that indicates any mesenchymal tumour arising in the gastrointestinal tract.

The recognition of the central role of *c-kit* mutations in the pathogenesis of GISTs (Hirota et al., 1998; Rubin et al., 2000) and in most cases the associated expression of KIT protein in these tumours has provided a reproducible genotypic and phenotypic marker (Kindblom et al., 1998). Therefore KIT (CD117 in the standardised terminology of leucocyte antigens) expression has emerged as a marker for discriminating GISTs from other mesenchymal

gastrointestinal neoplasms and some have equated immunoreactivity for KIT as definition of GISTs (Miettinen & Lasota, 2001).
Recently, it has become apparent that some GISTs that lacked *c-ki*t mutations were found to have activating mutations of *PDGFRA*. Therefore GISTs can be defined as specific CD117 positive and *c-kit* or *PDGFRA* mutation-driven mesenchymal tumours of the gastrointestinal tract.

2. Histogenesis

GISTs are either derived from or differentiate towards the interstitial cell of Cajal (ICC), or their stem cell precursors which have the capacity to differentiate towards both the ICC and smooth muscle phenotype (Kindblom et al., 1998; Rubin et al., 2000). The ICCs are intercalated between the autonomic nerves and smooth muscle cells. Their principle function is to generate autonomous rhythmic contractions, involved in digestion and peristalsis. Therefore these cells are known as the "pacemaker" cells of the gastrointestinal tract.
Morphologically, these cells are slender with ovoid nuclei and scanty cytoplasm. They have incomplete features of both neural and myoid differentiation.
Immunohistochemical studies revealed that GISTs have similar features to ICC, being positive with CD34 and CD117 and negative or variably positive for other neural and smooth muscle markers (Kindblom et al., 1998).

3. Molecular biology (*c-kit* and *PDGFRA*)

The *c-kit* proto-oncogene is a cellular homolog of the *v-kit* oncogene present in the genome of Hardy-Zuckerman-feline sarcoma virus (Besmer et al., 1986). It encodes a transmembrane tyrosine kinase receptor (Vliagoftis et al., 1997). The ligand for KIT is a growth factor called the stem cell factor.
Extracellular binding of stem cell factor results in dimerisation of the receptor, triggering phosphorylation of the kinase domain. This induces a signalling cascade that propagates through the cytoplasm into the nucleus. This signalling cascade affects many aspects of cellular behaviour including proliferation, differentiation, adhesion and apoptosis (Vliagoftis et al., 1997).
KIT expression is extremely important in the development of several cell types including the haematopoietic stem cells, mast cells, germ cells, melanocytes, some epithelial cells and the ICC (Vliagoftis et al., 1997).
The majority of GISTs have gain of function mutations of *c-kit* (Corless et al., 2004). These mutations have been observed in sporadic GISTs and less commonly as germline mutations in familial GISTs (Hirota et al., 1998; Isozaki et al., 2000), suggesting that constitutive expression of KIT plays a significant role in the tumourigenesis of GISTs. However, around 10-15% of GISTs lack *c-kit* mutations (Debiec-Rychter et al., 2004b). Within this group a large subset would have gain of function mutations of *PDGFRA* (Heinrich et al., 2003a; Heinrich et al., 2003b; Hirota et al., 2003).

3.1 *c-kit* mutations

Approximately 85%-90%of sporadic GISTs harbour a mutation of *c-kit* (Corless et al., 2002; Heinrich et al., 2002; Heinrich et al., 2003a; Hirota et al., 1998; Rubin et al., 2001). *c-kit*

contains a total of 21 exons. However, mutations cluster within only four exons. They are in decreasing order of frequency, exon 11 encoding the intracellular juxtamembrane domain, exon 9 encoding the extracellular domain , exon 13 encoding the first portion of the kinase domain and exon 17 encoding the kinase activation loop (Giuly et al., 2003; Heinrich et al., 2002) (Figure 1A).

Mutations affecting exon 11 have been reported in 60-70% of GISTs (Corless et al., 2002; Corless et al., 2004; Heinrich et al., 2003a; Hirota et al., 1998; Rubin et al., 2001). The juxtamembrane region exerts a negative regulatory effect on KIT receptor (Longley et al., 2001) and therefore mutations in this region lead to loss of its inhibitory function. Mutations in exon 11 are fairly heterogenous and different types of mutations cluster within different regions. These mutations correlate with the best response to imatinib.

Approximately 60-70% of exon 11 mutations are in-frame deletions of 1 to several codons and the majority occur at the 5' and cluster between codons Gln^{550} and Glu^{561} (Corless et al., 2004; Hirota et al., 1998).

Missense point mutations in exon 11 occur in 20-30% of GISTs. They affect codons Trp^{557}, Val^{559} and Val^{560} and Leu^{576}. Internal tandem duplications are found at the 3' end of the exon (codon 576-580) (Lasota et al., 2003a; Lasota & Miettinen, 2006; Rubin, 2006) and are typically seen in gastric GISTs (Lasota & Miettinen, 2006).

Exon 9 mutations are found in approximately 10% of cases (Antonescu et al., 2003; Hirota et al., 2001; Lasota et al., 2000b; Lux et al., 2000; Sakurai et al., 2001). Nearly all mutations affecting exon 9 are insertion of six nucleotides that result in Ala^{502}-Tyr^{503} duplication at the protein level (Heinrich et al., 2003a; Hostein et al., 2006; Lasota et al., 2000b; Lasota et al., 2003a; Lux et al., 2000; Willmore et al., 2004). This type of mutation is associated with small intestinal localisation and aggressive behaviour (Antonescu et al., 2003; Antonescu, 2006; Corless et al., 2004; Lasota et al., 2003a). Patients with this type of mutation respond less well to imatinib. More recently, another duplication leading to Phe^{506}-Phe^{508} duplication was reported (Heinrich et al., 2003a).

Mutations affecting exon 13 occur in approximately 1% of GISTs (Heinrich et al., 2003a; Kinoshita et al., 2003; Lasota et al., 2000b; Lux et al., 2000). All exon 13 mutations identified to date are missense mutations resulting in substitution of Glu for Lys^{642} (Lasota et al., 2000b; Lux et al., 2000) and are associated with resistance to imatinib treatment (Chen et al., 2004; Willmore et al., 2004).

Mutations affecting exon 17 are very rare and are found in less than 1% of all GISTs (Heinrich et al., 2003a; Rubin et al., 2001) and are typically missense substitution at codons 820 and 822 (Tornillo & Terracciano, 2006), whereas mutations at codon 817 are usually observed in non GISTs, including seminomas and mastocytomas (Corless et al., 2004).

3.2 *PDGFRA* mutations

Approximately 5%-10% of GISTs have mutations within *PDGFRA* (Corless et al., 2005; Heinrich et al., 2003b; Hirota et al., 2003). These mutations are functionally similar to *c-ki*t mutations and are usually seen in epithelioid, gastric GISTs which show weak or no immunoreactivity for KIT (Corless, 2004; Corless et al., 2004; Corless et al., 2005; Heinrich et al., 2003a; Hornick & Fletcher, 2007; Lasota et al., 2004; Medeiros et al., 2004). Three different regions of *PDGFRA* have been reported to be mutated in GISTs (Figure 1B). These mutations, in decreasing order of frequency affect exon 18, exon 12 and exon 14 (Corless et al., 2005; Heinrich et al., 2003b).

Exon 18 encodes the kinase activation loop (TK2). The majority of exon 18 mutations are missense mutations leading to substitution of Val for Asp[842]. These mutations are usually seen in gastric tumours and are associated with resistance to imatinib (Heinrich et al., 2003a; Heinrich et al., 2003b; Hirota et al., 2003; Hornick & Fletcher, 2007; Ohashi et al., 2004).
Exon 12 encodes the juxtamembrane. Mutations affecting exon 12 are rare and lead to Asp for Val[561] substitution. In-frame deletions and insertions have also been reported around codon Val[561] (Corless et al., 2005; Miettinen & Lasota, 2006b).
Exon 14 encodes the kinase I domain (TK1). A single missense mutation leading to substitution of Lys for Asn[659] has been described (Corless et al., 2005).
Approximately 5-10% of GISTs are negative for both *c-kit* and *PDGFRA* mutations. This subset of GISTs may have an activating mutation either in a tyrosine kinase receptor similar to KIT and PDGFRA or in downstream signalling molecule of KIT or PDGFRA signalling cascade (Hornick & Fletcher, 2007; Rubin, 2006).

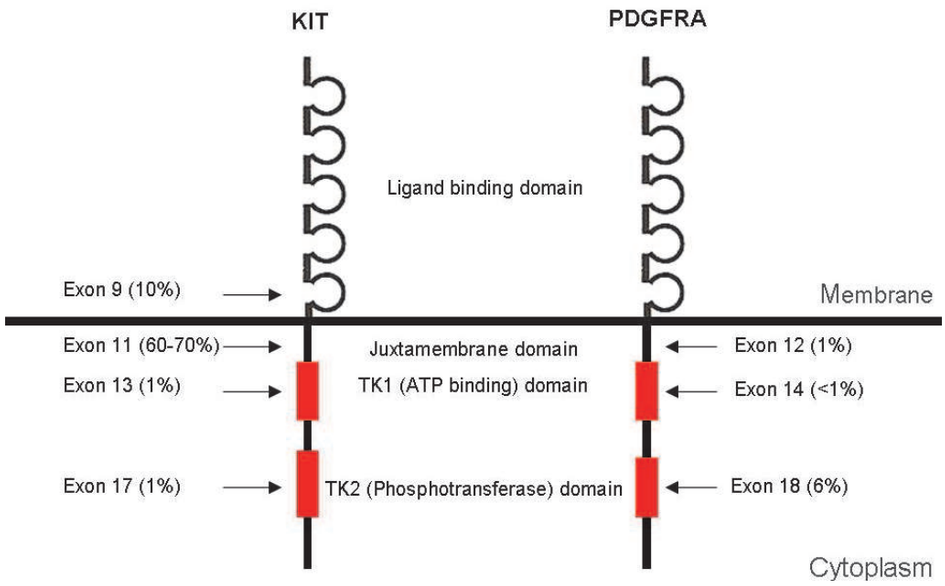

Fig. 1. Mutations of *c-kit* and *PDGFRA*.

3.3 *DOG1* gene

DOG1 "discovered on GIST" is a new gene, which encodes a protein of unknown function. It is expressed in GISTs independent of mutation type and is absent in non GISTs (West et al., 2004).

4. Epidemiology and risk factors

The lack of accepted diagnostic criteria for GISTs has led to variations in the current estimate of disease incidence. GIST is a relatively rare neoplasm representing less than 1% of all primary tumours of the gastrointestinal tract with an incidence of approximately 0.68-1.45/100,000 (Miettinen & Lasota, 2001; Nilsson et al., 2005; Tran et al., 2005). These figures do not account for benign GISTs, which are usually not included in cancer registries and are usually lost to clinical follow-up. Disease incidence seems to be uniform across all geographic and ethnic populations. More than 90% of GISTs occur in adults, mostly in middle-aged or

older individuals (Nilsson et al., 2005; Tran et al., 2005). There is no gender preference except in the setting of Carney's triad (Carney, 1999). Although there are no known predisposing risk factors, there are reports of familial GISTs (Isozaki et al., 2000) and GISTs in association with Von Recklinghausen's disease (Giuly et al., 2003), pointing to a genetic role.

Although GISTs may arise anywhere in the gastrointestinal tract, they are most common in the stomach (60%), followed by the jejenum and ileum (30%), duodenum (5%) and colorectum (<5%) (Miettinen & Lasota, 2006a; Miettinen & Lasota, 2006b). Very few cases have been described in the oesophagus (Miettinen et al., 2000a) or appendix (Miettinen & Sobin, 2001). A small proportion of GISTs arise in extra-gastrointestinal tract sites including the omentum, mesentery and retroperitoneum (Miettinen et al., 1999) with a few case reports of primary GISTs occurring in the gallbladder, pancreas, liver and urinary bladder (Bussolati, 2005; Hu et al., 2003; Lasota et al., 2000a; Mendoza-Marin et al., 2002). It is important to make sure that these do not represent spread from a primary lesion in the gastrointestinal tract.

5. GISTs syndromes

Although the vast majority of GISTs are sporadic, approximately 5% are associated with tumour syndromes. These include:

5.1 Familial GIST syndrome

This syndrome is inherited as an autosomal dominant disease. Patients with familial GISTs have germline activating mutations involving c-*kit* (Hirota et al., 2000; Isozaki et al., 2000; Li et al., 2005; Maeyama et al., 2001; Nishida et al., 1998; O'Brien et al., 1999) or *PDGFRA* (Chompret et al., 2004). These patients develop multiple GISTs, some of which in association with hyperplasia of the ICC (Chen et al., 2002). Other patients may also have the clinical manifestations of *c-kit* activation such as mastocytosis and hyperpigmentation (Kang et al., 2007).

5.2 Carney's triad and Carney Stratakis syndrome

Carney's triad consists of multicentric functioning extra-adrenal paraganglioma, pulmonary chondroma and multifocal epithelioid GIST of the stomach (Carney, 1999). There is a striking female predominance with approximately 85% of cases occurring in females. Most patients are less than 30 years of age at the time of diagnosis. Only subsets of patients have all of the three tumour types. Extra-adrenal pargangliomas and pulmonary chondromas may develop many years after the occurrence of GIST.

Carney Stratakis syndrome is a recently recognised autosomal dominant syndrome which represents a separate condition that affects both males and females and lacks the association with pulmonary chondromas. Mutations of the genes coding for succinate dehydrogenase subunits, typically associated with familial paragangliomas, are most likely implicated in the pathogenesis of Carney Stratakis syndrome (Pasini et al., 2008).

Mutations of *c-kit* or *PDGFRA* have not been identified in patients with Carney's triad or Carney Stratakis syndrome (Corless et al., 2004; Matyakhina et al., 2007; Prakash et al., 2005).

5.3 Neurofibromatosis type 1 (von Recklinghausen's disease)

Some patients with classic neurofibromatosis type 1 develop GISTs (Giuly et al., 2003; Takazawa et al., 2005). The tumours are usually in the small bowel and often multifocal.

They tend to be small, mitotically inactive and have a bland morphology. They are often accompanied by ICC hyperplasia. Most GISTs arising in the setting of NF1 do not have *c-kit* or *PDGFRA* mutations (Takazawa et al., 2005; Yantiss et al., 2005).

6. Clinical presentations

The clinical picture of GISTs depends on site, size and aggressiveness of these tumours which can vary from the benign to frank sarcoma. The symptoms can also vary, depending on the size and location of the lesion. Small tumours may be asymptomatic and may be found incidentally at laparotomy, endoscopy or during radiological studies for other conditions. Symptomatic tumours often present with abdominal pain or discomfort. They may ulcerate and cause gastrointestinal bleeding. This may be acute or insidious leading to anaemia or fatigue. Lesions in the oesophagus may present with dysphagia, while those of the intestine may present with an abdominal mass, obstruction or perforation. Occasionally, duodenal GISTs cause obstructive jaundice.

Patients with GISTs may also present with metastases, particularly to the liver. Malignancies reported in association with GISTs include carcinomas of the gastrointestinal tract as well as those of the breast, kidney, lung, uterus and prostate (Agaimy et al., 2006; Dematteo et al., 2000).

7. Morphology

7.1 Gross features

GISTs develop in any part of the gastrointestinal tract and tend to be primarily intramural tumours, usually involving the submucosa and muscularis propria.

GISTs vary in size from being several millimetres in diameter to over 30cms. Most lesions are well circumscribed, but are unencapsulated. Some are multinodular. They may have either a whorled fibroid-like cut surface or may be fleshy in appearance. They may protrude inward, leading to ulceration of the mucosa, or outward resulting in serosal based lesion. Large tumours may protrude into the lumen and from the serosa, resulting in a dumbbell appearance.

Areas of haemorrhage, cystic degeneration and central necrosis may be seen. The overlying mucosa may be intact or ulcerated, a feature that can be seen in either benign or malignant tumours.

7.2 Microscopic features

GISTs show a wide range of histologic features. Morphologically the cells of GISTs are spindle, epithelioid, mixed pattern and occasionally pleomorphic.

Spindle cell type is the predominant pattern, seen in 70% of GIST cases (Figure 2A). The tumour cells are arranged in short fascicles, whorls or a storiform growth pattern. The neoplastic cells have light fibrillary eosinophilic cytoplasm with indistinct cell borders. Perinuclear vacuoles are present and indent the nucleus at one pole (Figure 2B). These vacuoles are an artefact of fixation since they are not present in frozen sections (Appelman, 1977). The Nuclei tend to have relatively pointed ends as compared with blunt-ended nuclei in smooth muscle tumours, often with vesicular chromatin. Nuclear palisading reminiscent of that seen in schwannoma may be seen.

GISTs with epithelioid morphology account for 20% of cases (Figure 2C). The tumour cells are arranged in sheets or they may have a nested organoid growth pattern, reminiscent of

paraganglioma or carcinoid. The tumour cells exhibit eosinophilic or clear cytoplasm (Figure 2D). The cytoplasm may be retracted simulating inclusions. The nuclei tend to be round to ovoid and may be pushed to an eccentric location.

GISTs with a mixed pattern (Figure 2E) are more common in the stomach. It may feature an abrupt transition between spindle and epithelioid areas or may show intermediate ovoid cytologic appearance.

A small minority of GISTs (<5%) have extensive nuclear pleomorphism (Figure 2F).

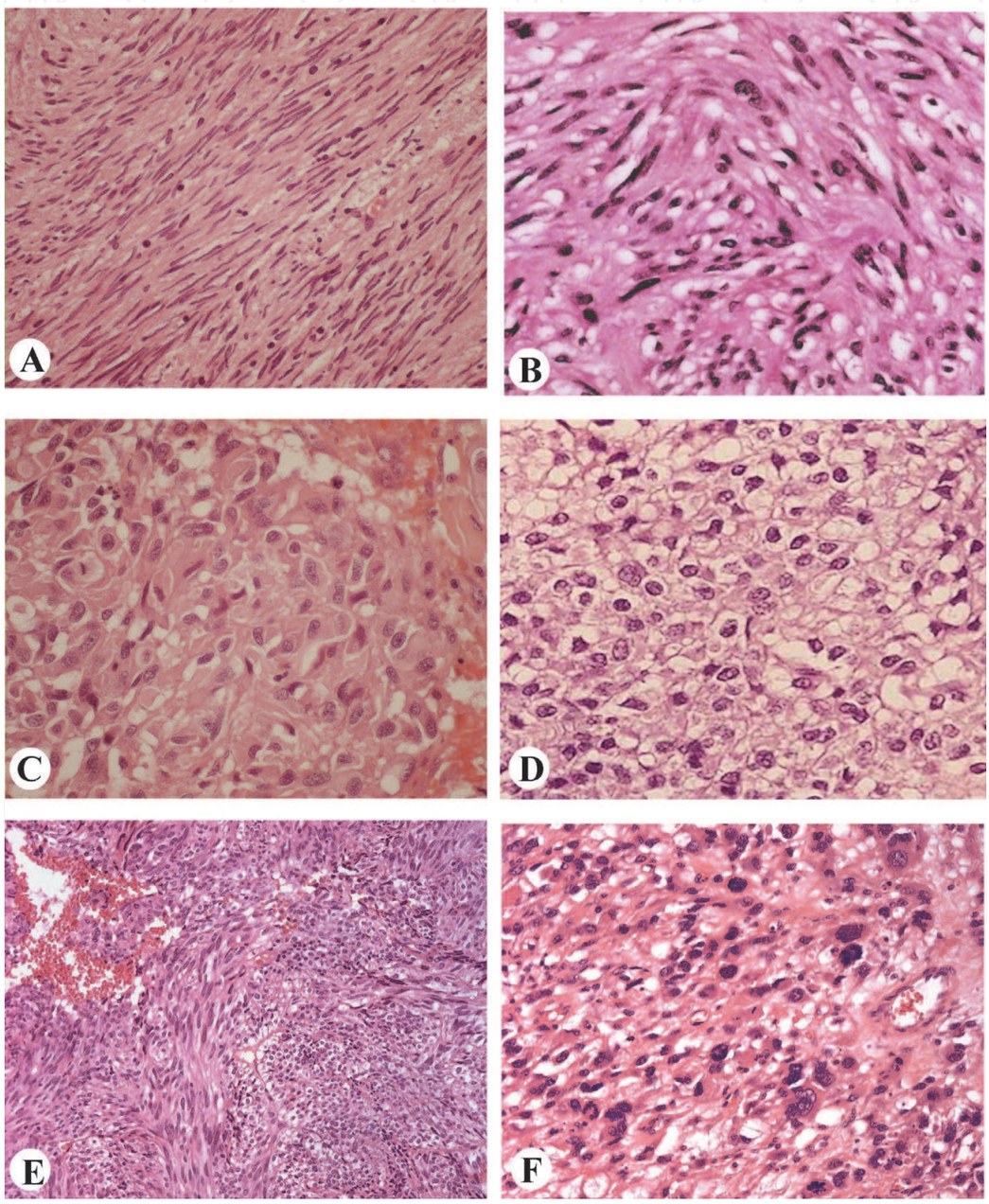

Fig. 2. Haematoxylin and Eosin sections of GISTs with a spindle cell morphology (A, B), GISTs with an epithelioid morphology (C, D), mixed cell pattern (E) and pleomorphic GIST (F).

The stroma in GISTs may be myxoid or it may be hyalinised (Figure 3A) or calcified. Delicate thin walled blood vessels may be prominent and may be associated with stromal haemorrhage (Figure 3B). Necrosis may be present. Lymphocytes can be seen.
Gastric GISTs have spindle cell morphology in 50% of cases, while 30% are epithelioid and 20% are mixed (Miettinen et al., 2005).
Small intestinal GISTs are more often spindled and may show extracellular bright eosinophilic collagen globules termed "skenoid fibres" (Figure 3C). These structures are periodic acid-Schiff (PAS) positive (Figure 3D). Small bowel tumours with an epithelioid morphology are usually associated with an aggressive behaviour.
Studies on oesophageal, colonic, ano-rectal and extra-gastrointestinal GISTs are sparse. Oesophageal GISTs involve the lower third of the oesophagus or gastro-oesophageal junction. They typically resemble gastric GISTs and usually show spindle cell morphology (Greenson, 2003). The majority of oesophageal GISTs are malignant.
Colonic GISTs and ano-rectal GISTs appear to be morphologically more similar to intestinal than gastric GISTs (Greenson, 2003). The majority are malignant with pleomorphic or overtly malignant spindle cell morphology.

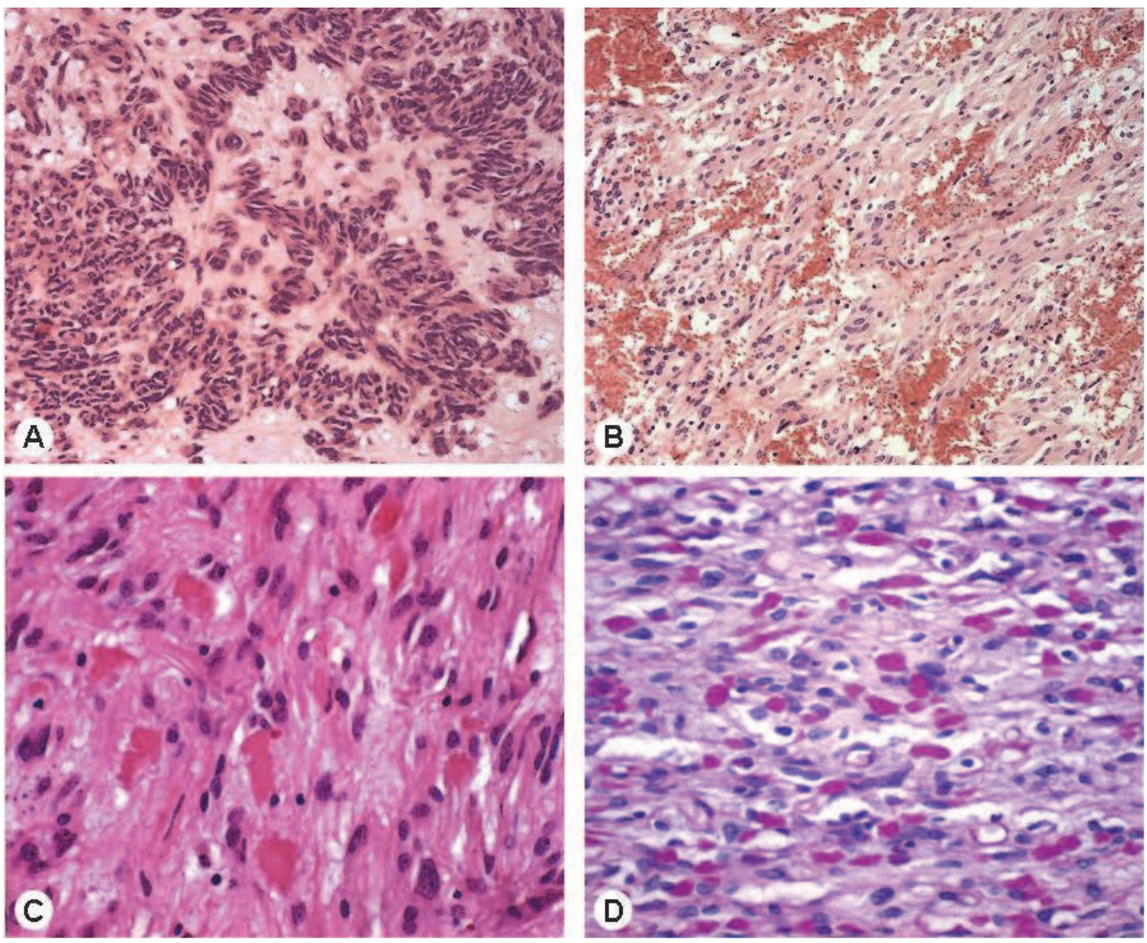

Fig. 3. GIST with a myxoid stroma (A), stromal haemorrhage (B), Skenoid fibres (C) and PAS positive skenoid fibres (D).

8. Gastrointestinal autonomic nerve tumours

GANTs were originally designated "plexoma" and "plexosarcoma" based on ultrastructural resemblance to cells of autonomic nervous system. GANTs are uncommon tumours which can occasionally develop in the context of von Recklinghausen's disease (Lespi & Drut, 1997) and Carney's triad (Segal et al., 1994). Familial multiple GANTs have been described in an association with intestinal neuronal dysplasia (O'Brien et al., 1999).
The characteristic ultrastructural features include complex interdigitating cell processes with bulbulous synaptic structures, dense core neurosecretory granules, rudimentary cell junctions and intermediate filaments.
Although originally believed to be a distinct tumour, recent evidence supports the concept that GANTs represent a phenotyptic variant of GISTs (Segal et al., 1994). These tumours tend to be KIT positive and a most have gain of function mutation in the juxtamembrane domain of *c-kit* (Lee et al., 2001).

9. Immunohistochemical features

The overwhelming majority of GISTs express KIT protein (detected as CD117). The results of KIT immunostaining depend on several technical factors including fixation, tissue preparation, variations in antibody clones in terms of specificity and sensitivity, antibody dilutions and staining techniques. This may account in part for the reported immunophenotypic heterogeneity in GISTs. It has been emphasised that CD117 should be performed without epitope retrieval (Fletcher & Fletcher, 2002).
The monoclonal antibodies currently available react inconsistently in formalin fixed paraffin embedded tissue and identify only a minority of GISTs (Miettinen et al., 2002b).
Given the potential clinical importance of CD117 immunostaining, optimisation of the staining techniques and reproducibility are critical.
The pattern of staining is variable (Figure 4). Diffuse strong pancytoplasmic staining is the predominant pattern. Membranous staining and dot-like "golgi zone pattern" staining can be identified. It has been suggested that different staining patterns correlate with different types of *c-kit* mutations (Fletcher et al., 2002a). Stromal mast cells and ICC are useful internal positive controls to supplement the normal positive and negative controls.

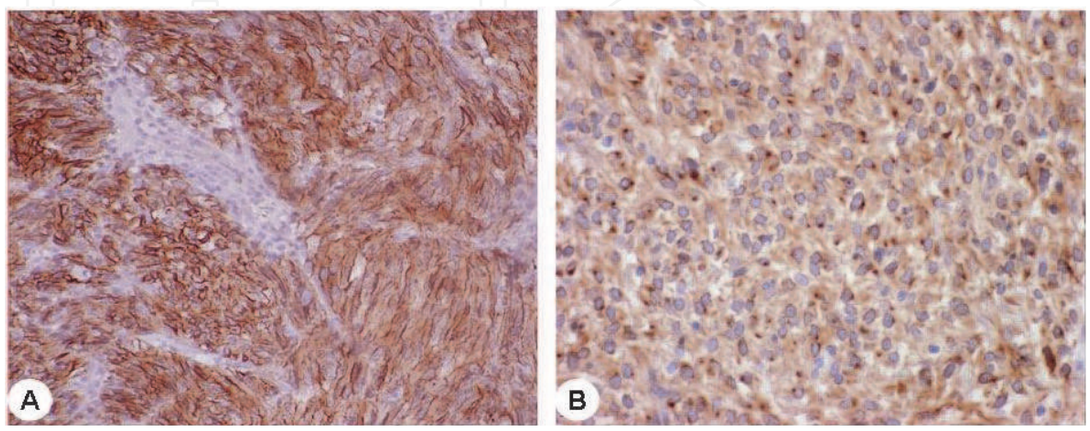

Fig. 4. Pattern of CD117 immunostaining. GIST showing membranous and cytoplasmic staining (A) and golgi zone-like staining (B).

Immunoreactivity may also be patchy, and thus false negative staining can be encountered in small biopsy specimens.

Immunohistochemical detection of KIT does not necessarily imply *c-kit* activation. Indeed CD117 is expressed by other tumour types such as melanoma and soft tissue sarcomas including dermatofibrosarcoma protuberans, synovial sarcoma and angiosarcoma (Sabah et al., 2003). The CD117 immunoreactivity should therefore, be interpreted in the context of morphology and clinical setting.

Approximately 5% of GISTs are KIT negative (Debiec-Rychter et al., 2004b; Medeiros et al., 2004). In these exceptional circumstances, KIT-negative mesenchymal lesions in the gastrointestinal tract with typical morphological features of GISTs may be referred to as "A stromal neoplasm most consistent with GIST". Such rare scenarios include GISTs that are either immunohistochemically inert for technical reasons, the subject of sampling error (biopsy of tumour with only focal KIT staining), the product of clonal evolution with emergence of KIT negative clone following imatinib therapy, or a rare example of a true GIST lacking KIT expression (Fletcher et al., 2002a; Parfitt et al., 2006). In such cases, pathologists should consider consultation with those experienced in dealing with large numbers of GISTs, as well as mutational analysis to look for mutations in *c-kit* and, if negative, *PDGFRA* (Corless et al., 2004; Medeiros et al., 2004).

DOG1 expression is found to be specific and sensitive for GISTs including KIT negative tumours (Espinosa et al., 2008; West et al., 2004). It has been reported in over 95% of cases.

CD34 is a transmembrane glycoprotein present on human haematopoietic progenitor cells and vascular endothelium. CD34 is detectable in approximately 60-70%. The oesophageal and rectal GISTs have the highest frequency of CD34 positivity, whereas small intestinal tumours have the lowest percentage of CD34 positivity (Miettinen et al., 2000b).

Muscle markers such as actin, calponin and h-caldesmon are positive in approximately 30% of cases (Miettinen et al., 2000b). α-smooth muscle actin (SMA) expression is often reciprocal with CD34 expression: the SMA positive tumours are often CD34 negative and vice versa. Some tumours may show mosaic pastern with actin positive and CD34 negative areas and vice versa (Miettinen et al., 2000b). Desmin positive immunostaining is uncommon (2%) (Fletcher et al., 2002a) and is often limited to scattered tumour cells. Prominent staining is more common in epithelioid tumours.

Positive staining for S100 protein occurs in 5-10% of GISTs, especially in small bowel tumours (Fletcher et al., 2002a). These tumours are usually negative for other neural markers including neurofilament and glial fibrillary protein.

Focal positive staining for cytokeratin markers can be seen especially in malignant epithelioid GISTs.

Data on immunohistochemical staining for PDGFRA protein are scant. Rossi et al (Rossi et al., 2005) evaluated the role of PDGFR immunohistochemistry in the differential diagnosis of KIT-negative GISTs. They reported positive expression of PDGFR, in KIT-negative GISTs, while KIT-positive GISTs, smooth muscle tumours, schwannomas and solitary fibrous tumours did not; however, 27% of desmoid tumours were also positive for PDGFRA. PDGFRA immunohistochemistry has not been standardised to be of practical diagnostic value in GISTs and many available antibodies do not appear reliable on paraffin-embedded material.

Protein kinase C theta (PKCθ) is a downstream effector in the KIT signalling pathway and has been suggested as an immunohistochemical marker for GISTs with a high specificity and sensitivity (Blay et al., 2004; Duensing et al., 2004). The expression of PKCθ has been

reported in 98% of GISTs, including several CD117- negative tumours (Motegi et al., 2005). However, experience with this marker is limited.

10. Differential diagnosis

The differential diagnosis of GISTs is wide and includes the following:

10.1 Smooth muscle tumours

Intramural leiomyomas are most common in the oesophagus, and in fact, leiomyomas in this location outnumber GISTs by 3:1 (Dow et al., 2006). Oesophageal leiomyomas arise typically in young men, usually in the lower third of the oesophagus. Intramural leiomyomas are rare in the stomach and small intestine, but are common in the colon (Miettinen et al., 2001). Muscularis mucosae leiomyomas are usually small polypoid lesions found incidentally at colonoscopy and are most often found in the colon and rectum (Miettinen et al., 2001).

Morphologically, leiomyomas are generally less cellular than GISTs and are composed of bland spindle cells with eosinophilic cytoplasm and cigar shaped nuclei. Rare cases may show nuclear atypia without mitotic activity. Calcifications may be seen. The cells are positive for desmin and actin and negative for CD117. Approximately 10-15% of smooth muscle tumours are positive for CD34 (Fletcher et al., 2002a).

Pelvic uterine leiomyomas may become attached to the colon and therefore may mimic GISTs. These tumours resemble uteric leiomyomas morphologically and are positive for actin and desmin. The tumours are also oestrogen and progesterone receptors positive, whereas GISTs are negative for hormonal receptors.

Leiomyomatosis peritonealis disseminate represents numerous small (2-3mm), smooth muscle nodules on the peritoneum (Tavassoli & Norris, 1982). The nodules are composed of smooth muscle cells with no atypia and low mitotic activity, usually less than 2/10 high power fields (HPFs) (Dow et al., 2006). The cells have similar immunohistochemical features to uterine leiomyoma (Dow et al., 2006).

Leiomyosarcomas of the gastrointestinal tract are rare. They usually occur in older adults with a female predilection and are most common in the colon (Dow et al., 2006). The tumour cells show nuclear pleomorphism, mitotic activity and necrosis. They are actin and desmin positive and CD117 negative.

10.2 Schwannoma

This is a rare mesenchymal tumours of the gastrointestinal tract. It occurs most frequently in the stomach with a peak incidence in 6th and 7th decades. The tumour typically involves the submucosa and the muscularis propria. Histologically, it appears as a sharply demarcated but unencapsulated lesion often surrounded by a lymphoid cuff. The tumour is usually small in size (< 5cm) and is composed of spindle cells with wavy nuclei and occasional intranuclear inclusions. Mitoses are rare (< 5/50 HPFs). The cells are positive for S100 protein. Antoni B areas may express CD34 (Fletcher et al., 2002a), however the cells are negative for CD117.

Gastrointestinal schwannoma lack *NF2* gene alterations found in many soft tissue schwannomas. In addition, they frequently exhibit glial fibrillary acidic protein (GFAP) which is not a feature in soft tissue sarcomas. On this basis, it has been suggested that

gastrointestinal schwannomas may represent a distinctive group of peripheral nerve sheath tumours (Lasota et al., 2003b).

10.3 Intra-abdominal fibromatosis

These are locally aggressive lesions but they usually do not metastasise. They occur either sporadically or in association with Gardner's syndrome, typically in young and middle-ages adults. Intra-abdominal fibromatoses are the most common primary tumours of the mesentery. The most common site is the mesentery of the small bowel, but some originate from the ileocolic mesentery, gastrocolic ligament or omentum. They may also occur in the reteroperitoneum and may involve the bowel wall. Most patients present with an asymptomatic mass, but some present with gastrointestinal bleeding or an acute abdomen secondary to bowel perforation.

These lesions are usually large in size, more than 10cm in diameter. Although grossly well circumscribed, they tend to infiltrate the surrounding tissue. Histologically, they are composed of spindle cell proliferation arranged in parallel with evenly spaced blood vessels. The stroma is typically collagenous with keloid-like fibres and thin-walled blood vessels. Mitotic figures can be identified.

CD117 has been reported to be positive depending on the antibody used (Miettinen, 2001; Yantiss et al., 2000). However, studies have suggested that under optimum technical conditions, intra-abdominal fibromatosis are CD117- negative tumours (Lucas et al., 2003). Nuclear immunoreactivity for β-catenin in these tumours has been reported to be useful in distinguishing these tumours from GISTs (Montgomery et al., 2002). CD34 is negative.

10.4 Inflammatory myofibroblastic tumour

Inflammatory myofibroblastic tumour known as "inflammatory psuedo tumour". The lesion often occurs in children but may be present in adults. It is commonly located on the peritoneal surface, but may involve the omentum, mesentery, stomach or intestinal wall. Patients with inflammatory myofibroblastic tumours present with abdominal pain and abdominal mass which may be associated with obstruction. Some patients present with fever, night sweats, malaise and weight loss. Whilst some of these lesions are felt to be benign reactions to infectious processes, others have been shown to be clonal in origin (Cook et al., 2001). Inflammatory myofibroblastic tumours are lobular or multinodular.

Histologically, they are characterised by spindled or stellate shaped cellular proliferation admixed with lymphocytes and plasma cells with streaks of fibrosis. The cells are positive for desmin and actin and negative for CD117 and CD34. A high proportion of these lesions are also positive for anaplastic lymphoma kinase (ALK1) (Cook et al., 2001).

10.5 Inflammatory fibroid polyp

This is a tumour-like lesion that occurs in adults and most often encountered in the small intestine, especially ileum and the stomach. The peak incidence is in the 6th to 7th decade of life. The lesion arises in the submucosa and is usually well circumscribed. It is composed of spindle cell proliferation admixed with granulation tissue-like blood vessels in a loose oedematous stroma. The cells may show concentric arrangement around the blood vessels, the so called "onion-skin pattern". Mixed inflammatory cells are present, comprising plasma cells, lymphocytes and mast cells. Eosinophils are usually prominent. The majority of these lesions are positive for CD34 but are negative for CD1117.

10.6 Solitary fibrous tumour

Solitary fibrous tumour may involve the peritoneal cavity and adhere to the bowel. It is characterised by a spindle cell proliferation admixed with collagen and "staghorn" blood vessels. The tumour cells are positive for CD34 but negative for CD117.

Predicting the clinical behaviour of solitary fibrous tumour is notoriously difficult, but large size, infiltrative margins, high cellularity, nuclear pleomorphism, tumour necrosis and high mitotic count (> 4/10 HPFs) are all associated with an increased risk of malignant behaviour (Gengler & Guillou, 2006).

10.7 Sclerosing mesenteritis

This tumour-like lesion affects the small bowel mesentery. It consists of fibrous bands infiltrating and encasing fat lobules with fat necrosis. Chronic inflammatory cells including lymphocytes, plasma cells and eosinophils are usually present. The cells are negative for CD34 and CD117.

10.8 Glomus tumours

These tumours rarely occur in the gastrointestinal tract. They are found almost exclusively in the stomach and mainly in women (Dow et al., 2006). They are usually benign and similar to peripheral glomus tumours. They are made up of round uniform cells arranged around prominent dilated haemangiopericytoma-like vessels. The cells are positive for smooth muscle actin and negative for desmin, S100 protein and CD117. CD34 positive staining is seen in 30% of cases (Miettinen et al., 2002c).

10.9 Miscellaneous lesions

GISTs with epithelioid morphology may be mistaken for paraganglioma, metastatic carcinoma, melanoma and clear cell sarcoma.

Paragangliomas arise outside the adrenal gland in approximately 10% of the cases. They occur anywhere along the midline of the retroperitoneum.

Metastatic carcinoma is the most common type of solid tumour of the mesentry and in most cases the primary site is an intra-abdominal neoplasm.

Malignant melanoma has a tendency to metastasise to the gastrointestinal tract. They are CD117 positive but can be distinguished from GISTs by the expression of S100 protein, HMB45 and Melan-A.

Clear cell sarcoma may rarely involve the gastrointestinal tract. The tumour cells are diffusely positive for S100 protein, but unlike peripheral clear cell sarcoma, they are negative for HMB45 and Melan-A. They are characterised by the presence of t(12;22) translocation with EWS-ATF1 gene fusions.

Mesothelioma with a sarcomatoid morphology may also mimic GIST if it involves the bowel. Mesothelioma cells are positive for calretinin and negative for CD34 and CD117.

Follicular dendritic cells sarcoma affects the spleen, but may extend into the adjacent structures. The tumour is composed of sheets and whorls of cells with ovoid nuclei. The cells are intimately associated with small lymphocytes and are positive for CD21 and CD35 and negative for CD117 and CD34.

Dedifferentiated retroperitoneal liposarcoma may be attached to the bowel wall and sometimes simulate GISTs. Thorough sampling usually reveals a lipomatous component.

Angiosarcoma can simulate GIST and can be positive for CD117, but the specific histologic and immunohistochemical features allow for the differential diagnosis from GIST.
Synovial sarcoma may rarely occur in the gastrointestinal tract, abdominal wall and retropeitoneum. Some immunohistochemical studies have shown KIT expression in synovial sarcomas (Sabah et al., 2003; Tamborini et al., 2001). However, synovial sarcoma exhibits (X;18) (p11.2;q11.2) translocation.

11. Prognostic factors

Several clinicopathological and cytogenetic features have prognostic relevance:

11.1 Clinicopathologic factors

11.1.1 Tumour stage at presentation

The presence of peritoneal or liver metastases at presentation is an adverse prognostic factor and is associated with a shorter survival (Dematteo et al., 2000). Invasion of adjacent organs also correlates with a poor outcome.

11.1.2 Tumour size, site and mitotic activity

The subset of GISTs that has a high likelihood of malignant behaviour is generally identified by increased tumour size and mitotic activity in the context of tumour location (Miettinen et al., 2002a; Miettinen et al., 2005; Miettinen et al., 2006; Miettinen & Lasota, 2006b). The size of the tumour should be measured along the greatest axis of the tumour. The mitotic count is most accurately expressed as the number of mitoses per 50 HPFs and should be performed on areas with highest mitotic activity. This requires adequate sampling of the tumour.
Based on the size of the tumour and mitotic count, GISTs can be classified into very low risk, low risk, intermediate risk and high risk (Fletcher et al., 2002a; Fletcher et al., 2002b) (Table 1).

GIST categories	Tumour size (cm)	Mitotic count (per 50 HPFs)
Very low risk	< 2	<5
Low risk	2-5	<5
Intermediate risk	<5 5-10	6-10 <5
High risk	> 5 > 10 Any size	> 5 Any mitotic rate > 10

Table 1. Tumour size and mitotic rate as guides to the evaluation of GIST malignancy (Fletcher et al., 2002b).

In recent years, it has become clear that GISTs require site evaluation because of differing behaviour (Emory et al., 1999; Miettinen et al., 2002a). It has been suggested that the site of the tumour is a prognostic factor independent of the tumour size and mitotic count (Emory et al., 1999) with small bowel tumours having the worst prognosis. This provided a rationale for the proposed site specific evaluation of GIST. In this classification, GIST is classified according to the site, size and mitotic count into three categories: benign, malignant and uncertain or low malignant potential (Miettinen et al., 2002a) (Table 2).

GIST categories	Criteria for diagnosis
Probably benign	**Intestinal tumours**: Maximum diameter ≤ 2 cm *and* no more than 5/50 HPFs **Gastric tumours**: Maximum diameter ≤ 5 cm *and* no more than 5/50 HPFs
Probably malignant	**Intestinal tumours**: Maximum diameter > 5 cm *or* more than 5/50 HPFs **Gastric tumours**: Maximum diameter > 10 cm *or* more than 5/50 HPFs
Uncertain (low malignant potential)	**Intestinal tumours**: Maximum diameter >2 cm but ≤ 5 cm *and* no more than 5/50 HPFs **Gastric tumours**: Maximum diameter > 5 cm and ≤ 10 cm *and* no more than 5/50 HPFs

Table 2. Tumour size, mitotic rate and tumour site as guides to the evaluation of GIST malignancy (Miettinen et al., 2002a).

Recent large series have evaluated the behaviour of large number of gastric and small intestinal GISTs. Because the data antedates imatinib application, it gives an insight into the natural history of GISTs. Based on the tumour size, mitotic count and the anatomic location of the tumour, GISTs are classified into different groups (Miettinen et al., 2005; Miettinen et al., 2006; Miettinen & Lasota, 2006b) (Table 3).

GIST groups	Tumour size (cm)	Mitotic count (per 50 HPFs)	Risk of progressive disease and malignant potential
1	≤ 2	≤5	Gastric: very low if any (0%) Small intestinal: very low if any (0%)
2	>2 ≤5	≤5	Gastric: low (1.9%) Small intestinal: low (4.3%)
3a	>5 ≤10	≤5	Gastric: low (3.6%) Small intestinal: intermediate (24%)
3b	> 10	≤5	Gastric: intermediate (12%) Small intestinal: high (52%)
4	≤ 2	> 5	Gastric: low (0% but too few cases to predict) Small intestinal: high (50% but too few cases to predict)
5	>2 ≤5	> 5	Gastric: intermediate (16%) Small intestinal: high (73%)
6a	>5 ≤10	> 5	Gastric: high (55%) Small intestinal: high (85%)
6b	> 10	> 5	Gastric: high (86%) Small intestinal: high (90%)

Table 3. Risk assessment of GISTs based on tumour size, mitotic count and tumour site (Miettinen & Lasota, 2006b).

A scheme proposed under the aegis of the National Institutes of Health (NIH) defined the risk of aggressive behaviour using the twin criteria of tumour size and mitotic activity count irrespective of tumour location. A significant body of opinion holds that the NIH scheme underestimates the risk of small bowel tumours and overestimates those of gastric origin. It is now widely held that this scheme should be replaced by one derived from the data collected by Lasota and Miettinen (Miettinen & Lasota, 2006a) (Table 4).
This scheme requires validation on independent data. Based on tumour size (maximum dimension in cm) and mitotic activity (number of mitoses per 50 HPFs), the categories of prognosis are defined as follows:

Tumour Parameters		Risk of progressive disease (metastasis or tumour-related death)			
Mitotic index ≤5/50HPFs	Size	Gastric	Duodenum	Jejenum/Ileum	Rectum
	≤ 2cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 - ≤5	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10	Low (3.6%)	Insufficient data	Moderate (24%)	Insufficient data
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
Mitotic index >5/50 HPFs	≤ 2cm	Insufficient data	Insufficient data	High (limited data)	High (54%)
	>2 - ≤5	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 - ≤10	High (55%)	Insufficient data	High (85%)	Insufficient data
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

Table 4. Risk stratification of GIST by mitotic count, tumour size and anatomic site (Miettinen & Lasota, 2006a).

11.1.3 Resection margins

The principal treatment for GISTs is surgery with wide local resection including a margin of 10–20mm for most tumours. Radical resection such as total gastrectomy with lymphadenectomy is not required. Involvement of the circumferential and surgical margins indicates a higher likelihood of local recurrence and therefore poorer outcome regardless of all other factors.

11.1.4 Epithelioid morphology

This cellular pattern is present in one third of gastric tumours, but is usually associated with more aggressive behaviour when found in the small intestine.

11.1.5 Mucosal invasion

Mucosal invasion is rarely seen in GISTs but is an adverse prognostic sign (Goldblum & Appelman, 1995) as it is confined to malignant GISTs (Miettinen et al., 2002a). Mucosal invasion should be distinguished from mucosal ulceration by its diffuse "lymphoma-like" pattern of growth between the glandular elements (Miettinen et al., 2002a). The presence of

mucosal ulceration has no prognostic significance as it is found in benign and malignant GISTs

11.1.6 Cellularity

Low cellularity has emerged as a favourable prognostic feature according to some studies (Goldblum & Appelman, 1995).

11.1.7 Nuclear pleomorphism

Marked nuclear pleomorphism in a spindle cell tumour suggests a malignant behavior, on the other hand, scattered bizarre multinucleated cells are characteristic of benign lesions.

11.1.8 Immunohistochemical markers

Proliferation markers (Ki-67, MIB-1 and proliferating cell nuclear antigen (PCNA)) may aid in tumour evaluation. It has been reported that tumours with more than 10% of nuclei for Ki-67 analogue are associated with metastases and poor survival rate (Amin et al., 1993; Panizo-Santos et al., 2000; Reith et al., 2000; Rudolph et al., 1998; Wang et al., 2002). One study has reported that MIB-1 index was not superior to mitotic count as a prognostic factor (Wong et al., 2003).

Alterations affecting certain cell cycle regulators have been implicated in the pathogenesis and tumour progression of many tumours.

The tumour suppressor gene $p16^{INK4}$ encodes a nuclear protein that belongs to the INK4A family of cyclin dependent kinase inhibitors and blocks cell cycle progression at the G1-S transition (Serrano et al., 1993). It has been reported that loss of p16 immunostaining is associated with high risk GISTs (Haller et al., 2005; Liang et al., 2007; Ricci et al., 2004; Sabah et al., 2004b; Sabah et al., 2006; Schneider-Stock et al., 2003; Schneider-Stock et al., 2005; Steigen et al., 2008).

Another gene, $p27^{KIP1}$ is also a cyclin dependent kinase inhibitor that belongs to the CIP/ KIP family. An inverse correlation between $p27^{KIP1}$ protein expression and the degree of malignancy has been observed. Low $p27^{KIP1}$ expression seems to be associated with aggressive clinical behaviour in GISTs (Gelen et al., 2003; Nemoto et al., 2006; Pruneri et al., 2003; Sabah et al., 2006).

E2F1 is a transcription factor. Phosphorylation of the Rb protein results in the release of E2F proteins, that are necessary for progression into S phase. Expression of E2F1 has been reported to be an adverse prognostic factor (Haller et al., 2005; Sabah et al., 2006).

Finally, the expression of p53, a transcription factor and a cell cycle regulator, has been extensively investigated in human malignancies including GISTs. Most studies have suggested that p53 expression correlates with histologically malignant GISTs (Al Bozom, 2001; Cunningham et al., 2001; Feakins, 2005; Gumurdulu et al., 2007; Haller et al., 2005; Hata et al., 2006; Hillemanns et al., 1998; Ryu et al., 2007; Sabah et al., 2006; Wang & Kou, 2007; Wang et al., 2002; Wong et al., 2003; Yalcinkaya et al., 2007).

11.2 Cytogenetic markers as prognostic factors

Prediction of clinical outcome on the basis of morphology alone is not always reliable. Other new and promising parameters that may aid prognostic evaluation may emerge from genetic studies.

11.2.1 Mutations of *c-kit* and *PDGFRA*

Both are known to be critical steps in initiating primary oncogenic events. The prognostic value and the therapeutic significance of *c-kit* mutations remain under investigation.

The presence of deletion/insertion mutations involving exon 11 has been identified as an independent negative predictor of disease-free survival (Lasota et al., 1999; Martin et al., 2005; Singer et al., 2002). In addition the type of *c-kit* mutation was found to be of prognostic relevance. For instance deletions; particularly deletions affecting codon 557 to 558 indicate a poor prognosis (Antonescu, 2006; Martin et al., 2005). In contrast, GIST patients harbouring point mutations or internal tandem duplications, follow a more indolent clinical course (Antonescu, 2006; Corless, 2004; Corless et al., 2004; Martin et al., 2005; Miettinen et al., 2005; Wardelmann et al., 2003).

Moreover an association between KIT exon 9 mutations and aggressive behaviour and non gastric site was reported (Antonescu et al., 2003; Corless et al., 2004).

It has been shown that the type of kinase receptor mutation influences response to imatinib treatment. Patients with GISTs expressing mutant exon 11 isoforms have a better response to STI-571 compared with patients harbouring mutations in exon 9 or without detectable *c-kit* or *PDGFRA* mutations (Heinrich et al., 2003a). In contrast, tumours with exon 17 or exon 13 mutations are primarily resistant to STI-571 (Chen et al., 2004; Debiec-Rychter et al., 2004a; Heinrich et al., 2003a; Tornillo & Terracciano, 2006). Similarly, mutations in exon 12 of *PDGFRA* have shown in vivo sensitivity to STI-571 compared with *PDGFRA* exon 18 (Debiec-Rychter et al., 2004a) which are resistant to both imatinib and sunitinib.

11.2.2 Chromosomal losses and gains

Certain cytogenetic aberrations have been identified in benign, malignant and metastatic GISTs, irrespective of their sites or degree of differentiation (Breiner et al., 2000; El Rifai et al., 1996; El Rifai et al., 2000; Gunawan et al., 2002; Kim et al., 2000; Lasota et al., 2005; Sandberg & Bridge, 2002; Sarlomo-Rikala et al., 1998; Wozniak et al., 2007), suggesting that these changes are early events in GIST tumourigenesis. These include losses at chromosome arms 14q and 22q.

Cytogenetic studies have reported correlations between the acquisition of additional chromosomal changes and aggressive behaviour such as gains at 5p and 20q and losses at chromosomes 1p, 9q and 9p. Gains at 8q and 17q have been detected in metastatic GISTs far more frequently than in primary tumours (Breiner et al., 2000; Debiec-Rychter et al., 2001; Derre et al., 2001; Gunawan et al., 2004; Kim et al., 2000; Miettinen et al., 2002a; O'Leary et al., 1999). Therefore, these chromosomal aberrations appear to be secondary events and may play an important role in tumour progression (Heinrich et al., 2003a) (Figure 5).

The loss of heterozygosity of the 9p region in malignant and low malignant potential GISTs has been investigated. It has been shown that loss of heterozygosity at the 9p region was absent in low malignant potential GISTs but was a common finding in high risk tumours (malignant and recurrent group). Recurrent GISTs showed more frequent deletions than their primary tumours (Sabah et al., 2004b). These findings support the theory that loss of 9p may contribute to the progression and/or malignant transformation of GISTs.

11.2.3 Telomerase activity

Telomerase is an enzyme that extends telomeric repeats on the ends of eukaryotic chromosomes, protecting them from loss, fusion and degradation. Most normal somatic

cells do not express telomerase. Telomerase activity has been detected exclusively in malignant GISTs (Gunther et al., 2000; Sakurai et al., 1998; Wang & Kou, 2007). The expression of human telomerase reverse transcriptase (hTERT) by immunohistochemistry was investigated and was found that hTERT expression occurs preferentially in malignant GISTs and that the signal intensity correlated with the mitotic count of the tumour (Sabah et al., 2004a).

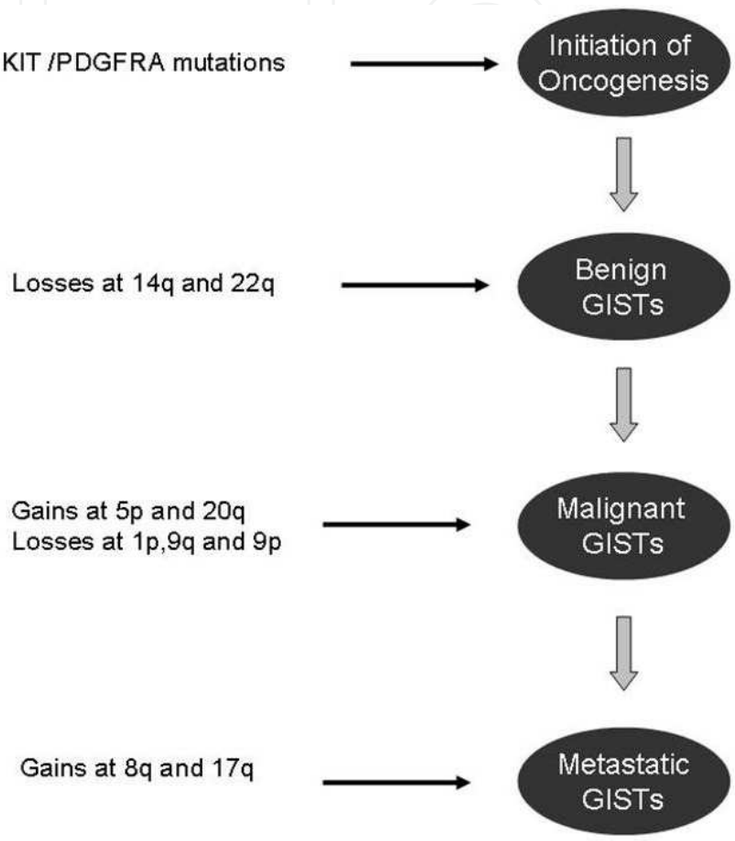

Fig. 5. Molecular events involved in the tumourigenesis of GISTs and chromosomal losses and gains involved in the progression of GISTs.

12. Imaging

Several radiological techniques are used to image GISTs. These include double contrast gastrointestinal X-ray series with barium, endoscopic ultrasound, computed tomography scanning and magnetic resonance. These modalities allow preoperative assessment of the size and involvement of other structures. They are also useful in identifying metastatic lesions.

Recently positron emission tomography (PET) scanning has been shown to be a useful and non-invasive mean of monitoring effectiveness of treatment of GISTs. Moreover, GIST response assessed by PET scan eight days after the start of imatinib mesylate treatment correlates with prognosis and survival at one year in patients with non-resectable GIST (Stroobants et al., 2003).

13. Treatment options

Until recently surgery was the only effective treatment for GISTs and complete surgical resection is still the only treatment that can cure the disease. However even for patients whose tumour was completely removed with clear margins there is still high probability of local recurrence.

Treatment options for recurrent or metastatic GISTs are even more limited. Radiation therapy is rarely used to treat GISTs because of the radio-sensitivity of adjacent organs and the high radio-resistance of these tumours. GISTs are highly resistant to conventional chemotherapy, regardless of the agent used. The reasons for this are not fully understood but may relate to the expression of the multidrug resistance protein products of the *MDR1* gene.

This bleak prognostic picture for patients with metastatic GISTs has recently changed with the advent of the tyrosine kinase inhibitor (STI-571, Imatinib mesylate). This drug binds to the ATP binding site of the target kinase and interrupts the signal transduction (Dematteo et al., 2002; Heinrich et al., 2002).

Imatinib is currently the first line agent for metastatic and unresectable GISTs and is currently under trial to test its possible effect of minimising the risk of recurrence in patients with high risk GISTs following complete resection (Dematteo et al., 2002). However, there is an ongoing debate on the duration, dose and the selection of patients for adjuvant therapy.

The effects of imatinib on GISTs morphology include reduction in tumour size, loss of cellularity, decreased mitoses or Ki67 proliferation index, degenerative changes such as myxoid stroma, cyst formation, necrosis and haemorrhage (Abdulkader et al., 2005; Loughrey et al., 2005; Pauwels et al., 2005). Additional potential diagnostic pitfalls include a possible shift from spindled to epithelioid morphology, loss of KIT and CD34 immunoreactivity (Abdulkader et al., 2005; Loughrey et al., 2005; Pauwels et al., 2005; Sciot & Debiec-Rychter, 2006) and positive desmin immunostaining in a tumours which were previously completely negative for desmin (Sciot & Debiec-Rychter, 2006).

Some 90% of patients obtain symptomatic relief. About two thirds achieve an objective response, as defined by a reduction of 50% or greater in tumour volume (van Oosterom et al., 2001). Another 20% of patients remain stable. However, in 10% the disease progresses despite of imatinib therapy due the occurrence of secondary mutations or clonal selection which cause drug resistance.

In such cases other tyrosine kinase inhibitors or downstream targets such as protein kinase theta can be tried (Sakamoto, 2004). Sunitinib malate (SU11248) has shown promising activity in imatinib resistant GISTs. In addition to KIT and PDGFRA, this drug also targets FLT3 and VEGF receptors (Demetri et al., 2003; Sakamoto, 2004).

Other drugs that are being evaluated in imatinib-refractory patients include Nilotinib (Montemurro et al., 2009) (inhibitor of KIT and PDGFRA); Sorafenib (a multi kinase inhibitor of raf kinase, VEGFR, PDGFR and KIT)(Demetri, 2011); RAD001 (a rapamycin analogue inhibitor of the protein kinase mammalian target of rapamycin); Oblimersen (an antisense oligonucleotide to bcl-2 mRNA); heat shock protein 90 inhibitor (17-allyylamino-18-demethoxy-geldanamycin, 17-AAG) (Bauer et al., 2006); Bevacizumab (a neutralising antibody to vascular endothelial growth factor); CCI 779 (a rapamycin analogue inhibitor of the protein kinase mammalian target of rapamycin); PKC 412 (an inhibitor of protein kinase C) and neutralising antibodies against vascular endothelial growth factor and several multi kinase inhibitors (De Giorgi & Verweij, 2005; Rubin, 2006).

14. Conclusion

GISTs constitute the largest group of mesenchymal tumours of the gastrointestinal tract. These tumours originate from the ICC or their precursors. Most GISTs express KIT and have gain of function mutations of *c-kit* or *PDGFRA*. Therefore, KIT expression has emerged as an important defining feature for these tumours. However, KIT expression is not specific for GISTs and should be interpreted in the context of clinical setting and appropriate morphology. A minority of GISTs are negative for KIT. In such cases, analysis of *c-kit o*r *PDGFRA* genes is necessary for accurate diagnosis. Clinically and pathologically, GISTs represent a spectrum of tumours that include benign, malignant and borderline variants.
Prognostic features indicative of malignancy or high risk for aggressive clinical behaviour are generally identified by increased tumour size and mitotic activity in the context of tumour location. Cytogenetic parameters aid prognostic evaluation and may play a role in the prognostication of GISTS in the future.
Imatinib has revolutionised the management of advanced and metastatic GISTs. Alternative therapeutic strategies are currently being evaluated. These may benefit patients who are refractory to imatinib or may be useful as adjuvant/neoadjuvant therapy to improve the outlook for GIST patients.

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Soft tissue tumors include a heterogeneous group of diagnostic entities, most of them benign in nature and behavior. Malignant entities, soft tissue sarcomas, are rare tumors that account for1% of all malignancies. These are predominantly tumors of adults, but 15% arise in children and adolescents. The wide biological diversity of soft tissue tumors, combined with their high incidence and potential morbidity and mortality represent challenges to contemporary researches, both at the level of basic and clinical science. Determining whether a soft tissue mass is benign or malignant is vital for appropriate management. This book is the result of collaboration between several authors, experts in their fields; they succeeded in translating the complexity of soft tissue tumors and the diversity in the diagnosis and management of these tumors.

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