Gastrointestinal Stromal Tumors (GISTs)

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Soft Tissue Sarcoma, GIST and Neuroendocrine Neoplasms

Contents

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Learning Objectives

By the end of this chapter, the reader will:

- Have learned the basic concepts of epidemiology, histological subtype, and molecular profile of gastrointestinal stromal tumors (GISTs).
- Have reached in-depth knowledge of diagnosis, staging, and clinical management of gist.
- Be able to put acquired knowledge on GIST into clinical practice

59.1 The Role of Medical Treatment in the Management of GIST

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59.1.1 Introduction

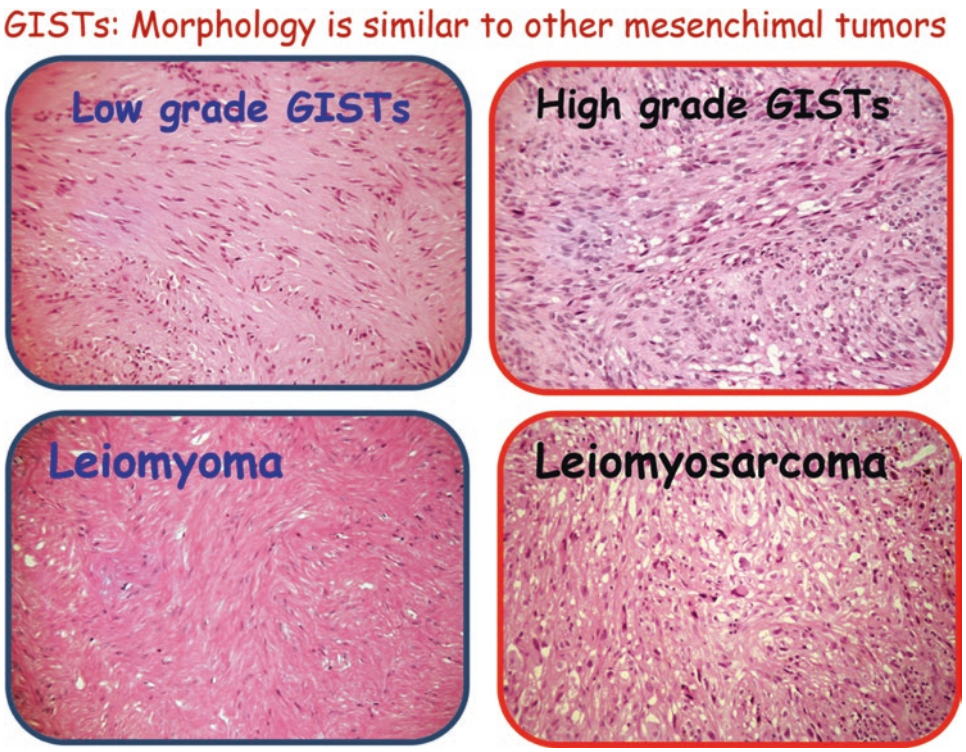
GISTs, while *relatively rare*, are the most common primary mesenchymal neoplasms of the gastrointestinal tract.

GISTs are typically *highly resistant to conventional chemotherapy*; the discovery of activating mutations in the *proto-oncogene KIT* and the development of *tyrosine kinase inhibitors* (*TKI*), such as imatinib, first introduced in 2002, revolutionized the treatment strategy for GISTs, by making possible to target the specific molecular events that are key events for pathogenesis of the disease.

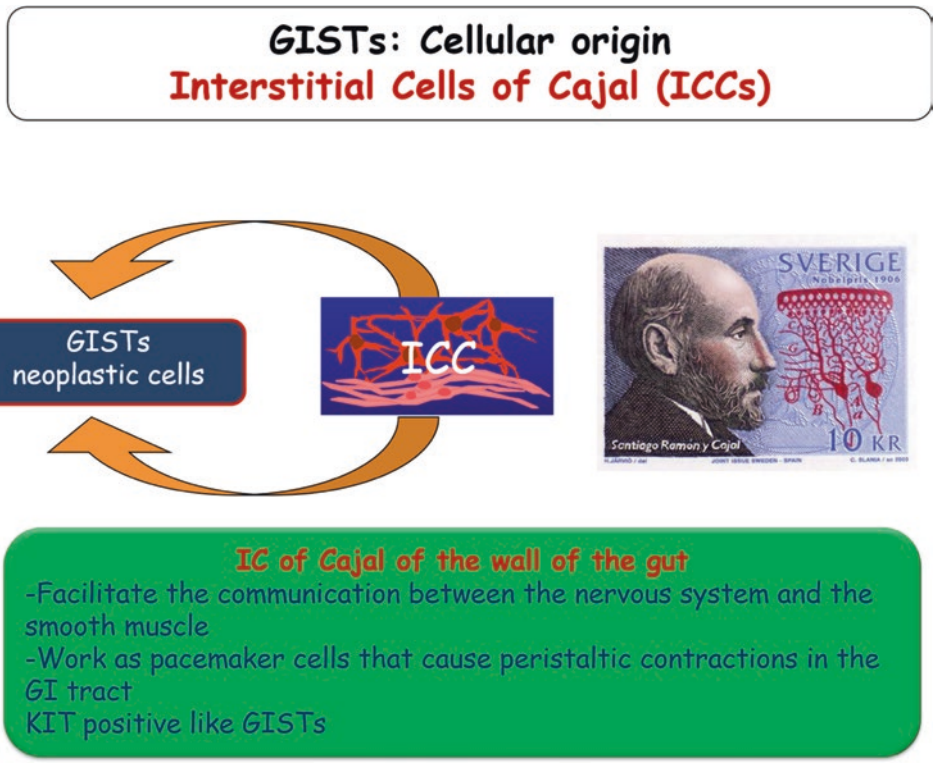
- GISTs can arise at *any age*, with a median of diagnosis *around 60–65 years.*
- More than 80% of the patients are older than 50 years.
- Occurrence in children is rare, and pediatric GIST represents a distinct subset, with the absence of KIT/platelet-derived growth factor alpha (PDGFRA) mutations, female predominance, and multifocal pattern of gastric GISTs [1, 2].
- GISTs can be found *anywhere in the gastrointestinal tract*, but the most frequent location is stomach (55%), followed by small intestine (30%). Less frequent are colon/ rectum (5%) and esophagus (<1%).
- Exceptionally rarely, GISTs can occur outside the gastrointestinal tract, such as in the omentum, mesentery, or retroperitoneal (<5%) (Fig. 59.1).

59.1.2 Origin

For many years, GISTs were initially classified as smooth muscle sarcomas, such as leiomyoma, leiomyoblastoma, or leiomyosarcomas.



Further studies identified similarity to a cell population in the gastrointestinal tract called *interstitial cells of Cajal* (*ICCs*), present in the wall of the gut. These cells facilitate the communication between the nervous system and the smooth muscle and work as pacemaker cells that cause peristaltic contractions in the GI tract. Data proving this relationship are based on similar histological findings and above all on the common expression of certain antigens such as CD117, the product of the oncogene c-KIT, and myoid antigens [3].



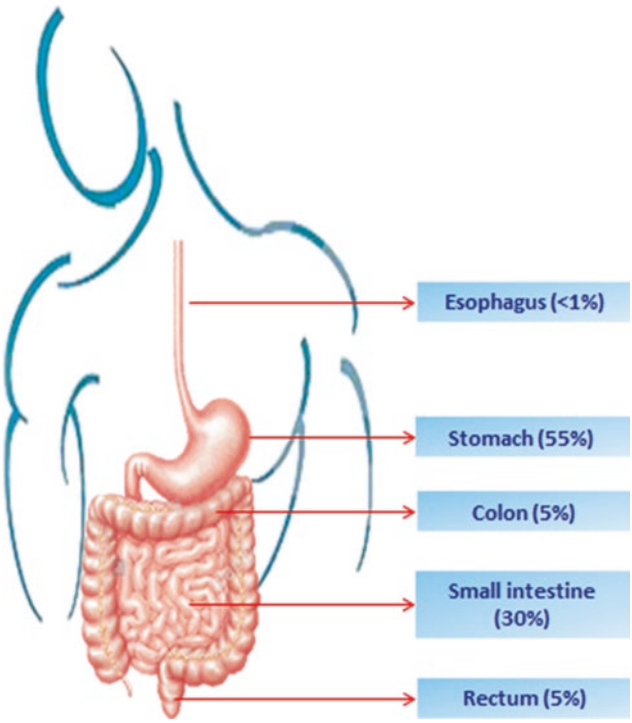


Fig. 59.1 GISTs distribution on the gastrointestinal tract

59.1.3 Pathological Features

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry.

59.1.3.1 Macroscopic Aspects (Fig. 59.2)

59.1.3.2 Microscopic Aspects and Immunohistochemistry (IHC)

A. Microscopic evaluation reveals *three principal subtypes of GIST* depending on the cytomorphology: spindle cell, epithelioid cell, and the less frequent GISTs with mixed morphology, both spindle and epithelioid cells (Fig. 59.3).
B. Approximately, the *95%* GISTs are immunohistochemically *positive for the tyrosine kinase receptor KIT (CD117)*. About 5% of GISTs are, instead, negative for detectable KIT expression [4].
C. In the diagnosis of c-kit-negative cases, DOG1 expression is a new immunohistochemical marker with unknown functions selectively expressed in GISTs.

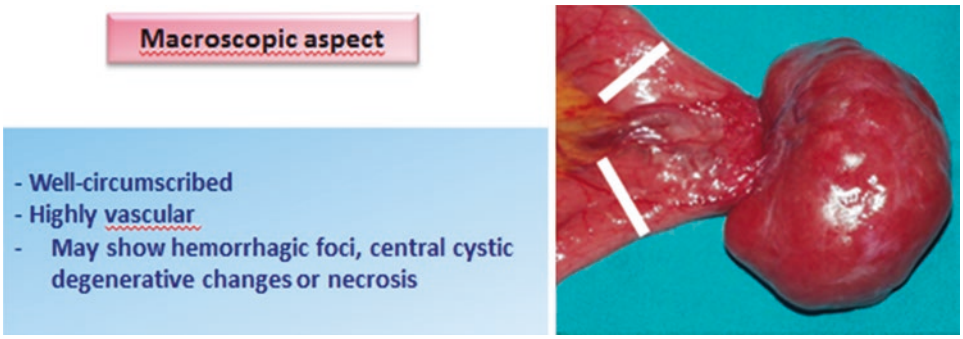


Fig. 59.2 Macroscopic appearance of a small bowel GIST. (Courtesy of Dr. A. Gronchi)

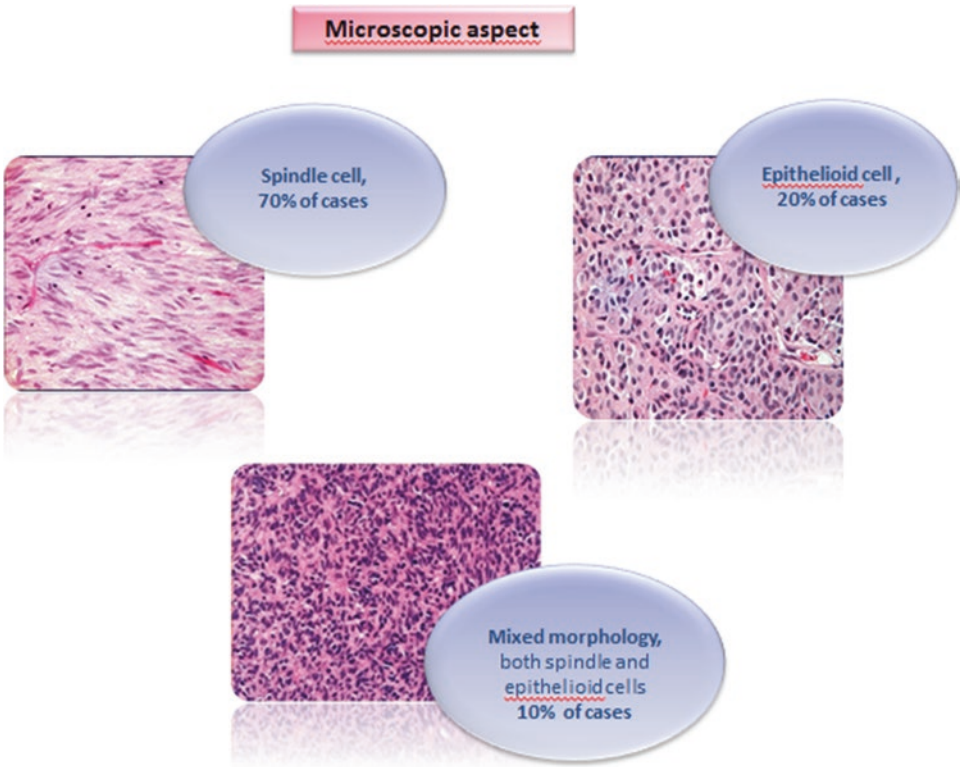
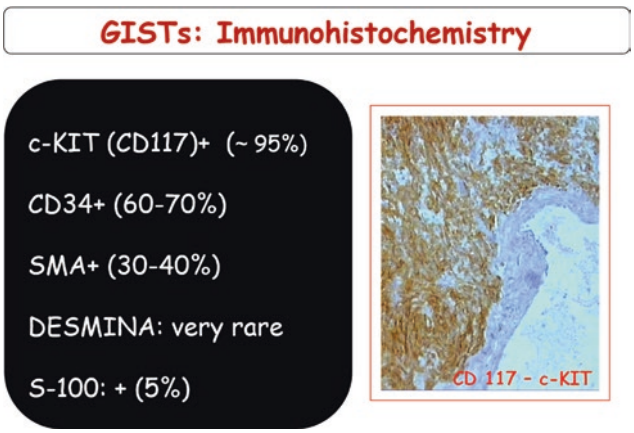


Fig. 59.3 Histological subtype of GISTs

Because the receptor KIT (CD117) is commonly expressed on GIST cells, it represents an important feature for a correct histological diagnosis [5]. Other antigens to be studied are CD34, an antigen common in hematopoietic stem cells, endotheliocytes, and fibroblasts, positive in 70–80% of GISTs, smooth muscle actin (SMA) positive in around 30% of GISTs, and usually reciprocal to CD34 and vimentin, while S100 and desmin expression is usually rare [2, 3].



59.1.4 Molecular Biology

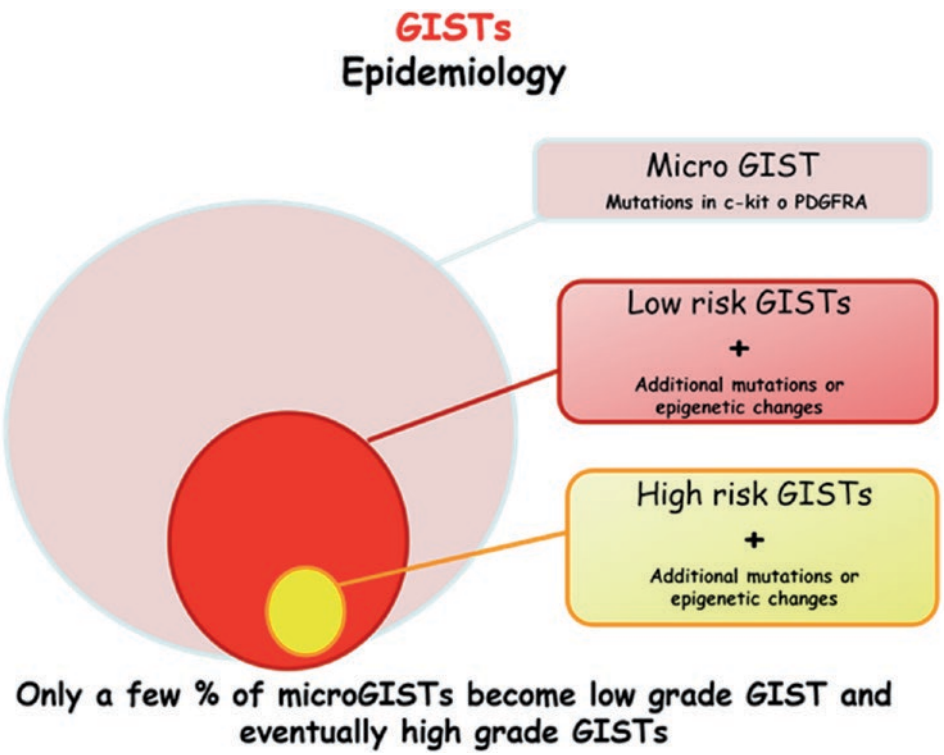
The identification of *activating mutations in the proto-oncogene KIT* in 1998 triggered a sea change in our understanding of the GIST pathogenesis and has resulted in a new paradigm for the use of molecular genetic diagnostics to guide targeted therapies.

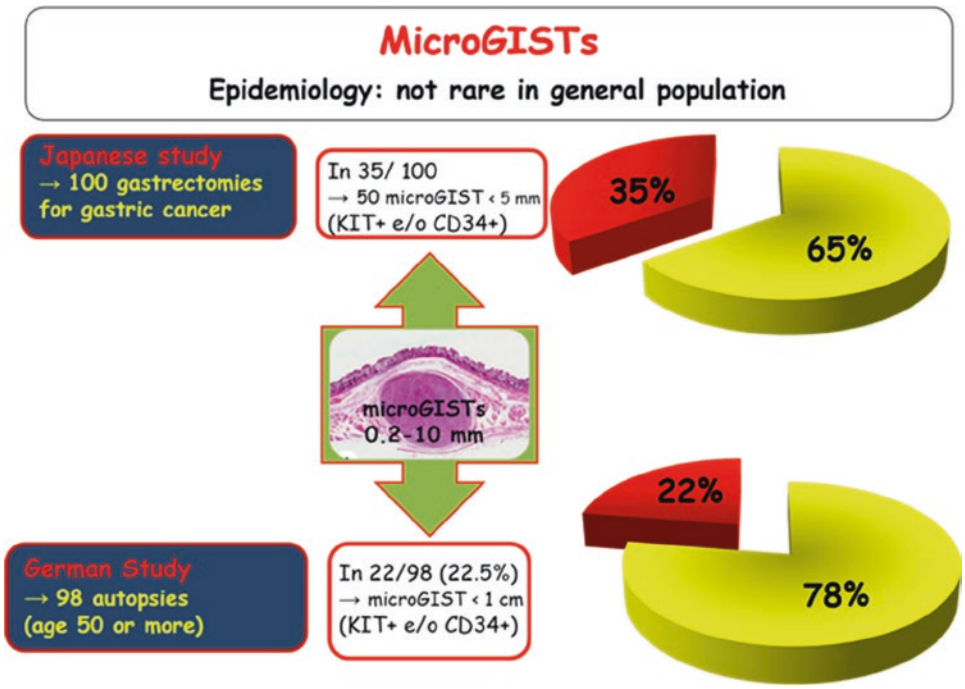
KIT gain-of-function mutations, together with those in *platelet-derived growth factor receptor A* (*PDGFRA*), are now well established as the *driver mutations* in the majority of GISTs [3, 6].

While pediatric and Mendelian inheritance-based GISTs are often wild type for PDGFRα and C-KIT and may be mutated in other genes such as *SDH*, sporadic GISTs often need a mutation of these genes as a fundamental step in their pathogenesis [7].

However, KIT and PDGFRα mutations are not sufficient for the development of a high-risk GIST since it seems other mutations or chromosomal aberrations are required. In fact, similar to the carcinogenetic model hypothesized for colon cancer by Vogelstein, a model of tumor evolution has also been proposed for GIST, that is, the high-risk GIST commonly seen in clinical practice would be the result of the evolution of a micro-GIST, usually characterized by the mutation of C-KIT or PDGFRα, to a low-risk GIST by acquiring new mutations such as secondary point mutations or epigenetic alterations and then to a clinically evident disease by new KIT or PDGFRα activating mutations, telomerase activation, or chromosomal aberrations [8].

Furthermore, the so-called micro-GISTs are probably extremely common in the population – about 30% in different studies – though only a very small number of these will progress to low- and then high-risk GISTs [9, 10].





The *frequency* of mutations in KIT and PDGFRA is different, and the mutations are mutually exclusive [11]:

- *Approximately 70%* of GISTs are driven by mutations in the *oncogene KIT.*
- Of those GISTs without KIT mutations, the majority harbor mutations in the gene encoding (*PDGFRA*) (15%).
- The remaining 15% of GISTs initially were genetically unclassified and described as KIT/PDGFRA "wild-type" GISTs. Today, with the expansion of our knowledge about molecular profile, further different and less frequent genetic mutations in other genes, such as *BRAF* and *KRAS,* have been recognized.

Therefore, at the state of current knowledge of molecular spectrum of mutations, GISTs can be divided into two distinct clusters: *succinate dehydrogenase (SDH)-competent* and *SDH-deficient subgroups*, each with distinct clinical and genetic characteristics (◘ Fig. 59.4) [3, 12].

1. *SDH-Competent GISTs*
   Heterogeneous group of tumors that primarily comprises KIT/PDGFRA/BRAF/NF1-mutated GISTs with normal genomic methylation patterns, in most cases presenting as sporadic tumors.
2. *SDH-Deficient GISTs*
   Characterized by a pattern of global, genome-wide DNA hypermethylation and are diagnosed primarily in pediatric patients or young adults. SDH-deficient GISTs almost always arise in the stomach, show prevalent epithelioid histology, and undergo early metastasis to liver and lymph nodes, with a relatively indolent long-term course [13].

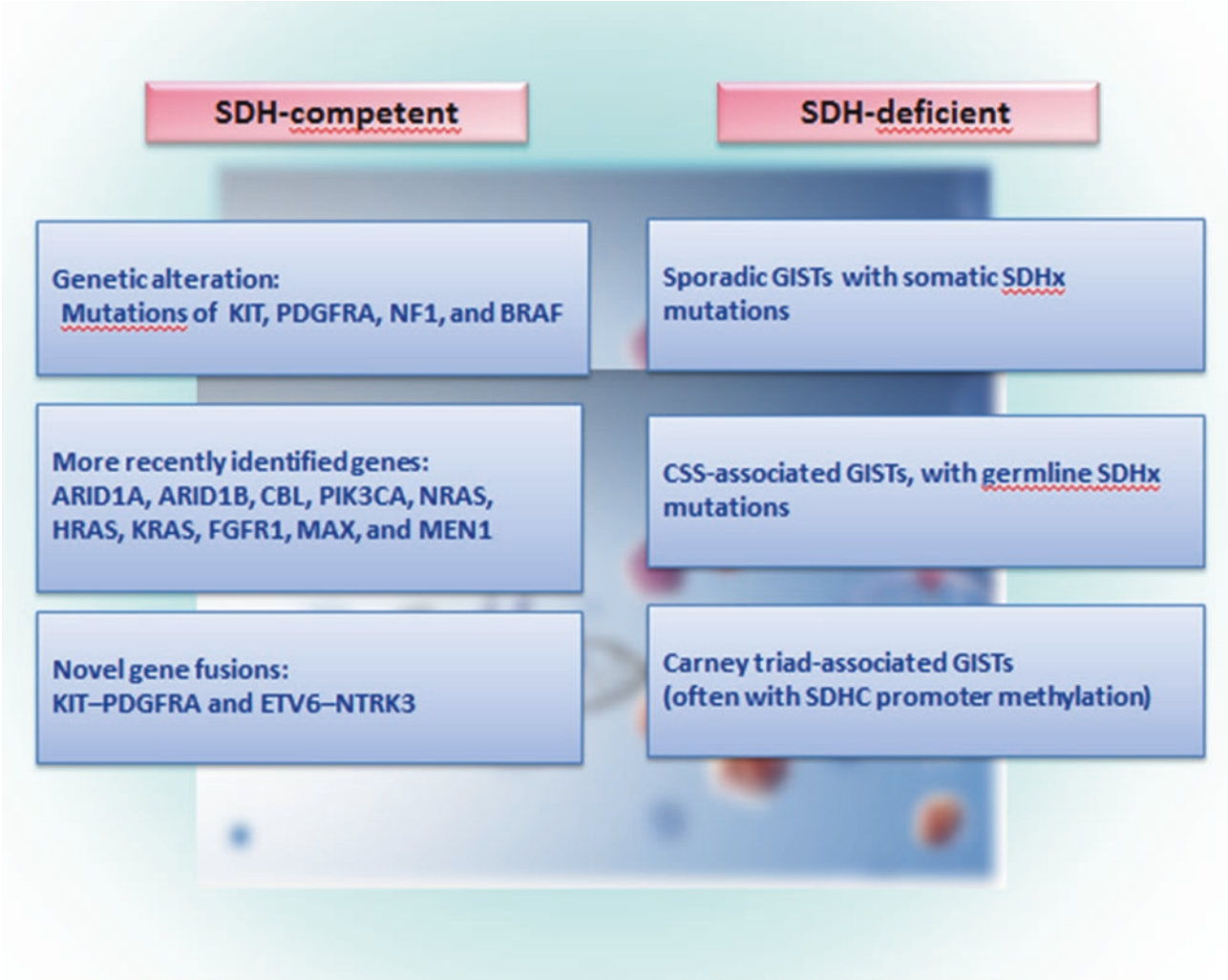
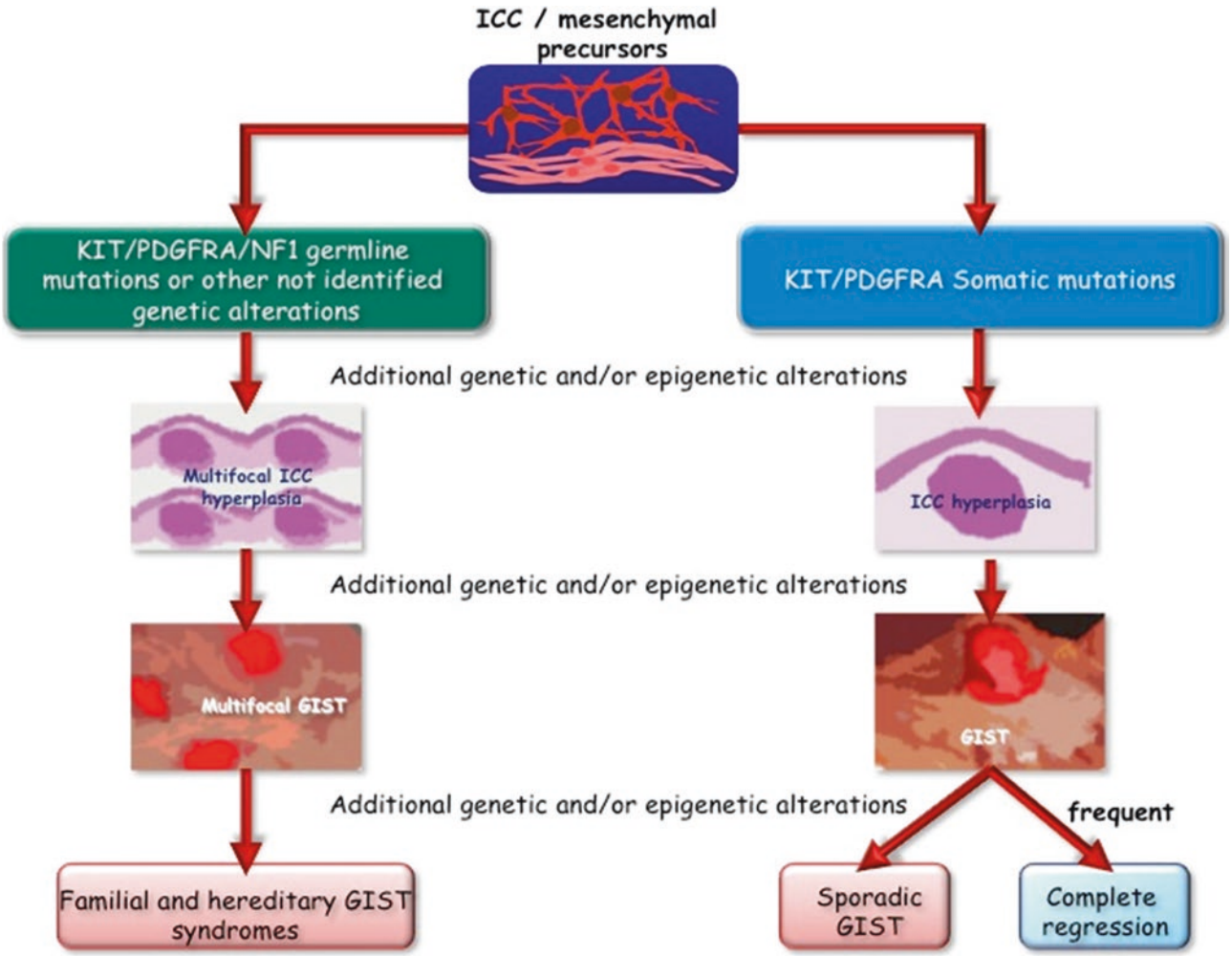


Fig. 59.4 Succinate dehydrogenase (SDH)-competent and SDH-deficient subgroups of GISTs

Features	Corney's triad	Corney's-Stratakis diad
GISTs	yes	yes
Paraganglioma	yes	yes
Pulmonary chondroma	yes	No
Hereditary	No	yes
Gender	> F	F = M
c-Kit or PDGFRA mutations	yes	No
Mutations on the SDH subunits SDHD, SDHC and SDHB	yes	In 9/11 families
SDH gene loss	In some cases	In some cases

Biology of Familial GISTs The initial role of mutations leading to the acquisition of function by the genes KIT or PDGFRA in the oncogenesis of GISTs is suggested by their transmission through the germinal line in different familial cases. Germinal mutations in these genes have been observed in 14 families. The mean age at diagnosis in patients with familial GISTs is 46 years. This familial form is not so common in children. Nevertheless, it is important to evaluate patients according to the effects and symptoms associated with germinal mutations in the genes KIT and PDGFRA, which include melanomas, freckles, urticaria pigmentosa, perioral and perianal hyperpigmentation, and achalasia. The various clinical manifestations in patients with germinal mutations in KIT are closely dependent on the specific domain of the KIT involved in the mutation. Aberrant mutations affecting the juxtamembrane domain (exon 11) are associated with mastocytosis and hyperpigmentation, apart from the generalized hyperplasia of the progenitor intestinal Cajal cells (ICC). Nevertheless, such symptoms do not seem to be present when the mutation involves the kinasic activity domain.

The initial phases of familial GISTs appear biologically similar to those of sporadic GISTs, with similar cytogenetic progression mechanisms and genic expression profiles.

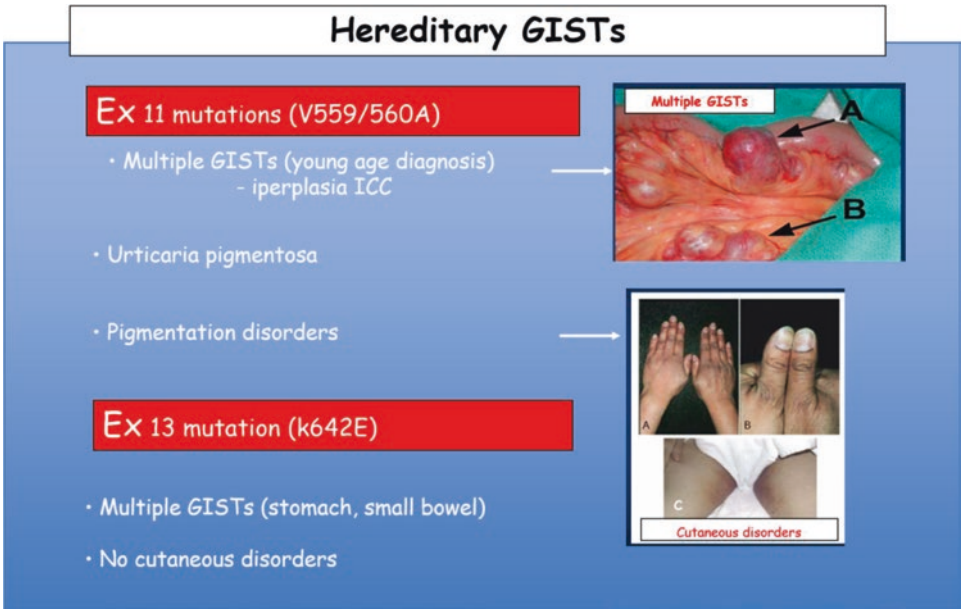


In familial GISTs, germinal mutations in KIT and PDGFRA are mostly similar to those found in sporadic forms. Two mutations which have never been found in sporadic GISTs, Asp419del in KIT and Tyr555Cys in PDGFRA, have, however, been identified in two families presenting hereditary GISTs. Furthermore, a recent study reports the case of a patient who developed lipomas and GISTs and who showed the germinal mutation Asp561Val in PDGFRA.

Two very similar models of transgenic mice have been developed in an attempt to identify the germinal mutations of KIT found in familial GIST syndromes

63. Such mutations are exactly the same as those found in patients with sporadic GISTs. Transgenic mice with these mutations maintain both their vitality and fertility and develop GISTs with a penetrance of about 100% 64.

The first case of familial GIST observed involved a Japanese family where the deletion of one of the two consecutive residues of valine (codon 559 or 560, GTTGTT) in exon 11 of KIT was identified throughout three generations. The subjects affected presented perianal hyperpigmentation and developed both malignant and benign multiple GISTs 65. A germinal mutation in the kinasic domain I of KIT has been identified in France in a 67-year-old woman and her 40-year-old son. Both these patients presented a dozen duodenal and jejunal GISTs and presented a constitutive substitution (K642E) in exon 13 of KIT 66 [10].



GISTs are not often diagnosed in children. Up till now, pediatric forms make up only 1% of all the identified cases. The current know-how regarding adult GISTs and correlated tumors, for example, paragangliomas, together with the development of new methods, such as microarray techniques, have led to remarkable progress in the comprehension of the rare pediatric forms. These may, however, show a different pathogenesis from that of adult GISTs, since apparently no mutations of *KIT* and *PDGFRA* are present (*wild-type* GIST). This might indicate that there exist other activation mechanisms of *KIT* or oncogenic *pathways* which are not linked to the gene and which are active within the cells. In the majority of pediatric GISTs examined, no other cytogenetic anomaly or alterations of exons 9, 11, or 13 of *KIT* have been identified. Of the 64 pediatric GISTs undergoing mutational analysis reported in literature, only 7 (11%) show a mutation in the genes *KIT* and *PDGFRA*. These mutations were equally distributed between exons 11 and 9 of *KIT* and were relatively common in *PDGFRA*. A homozygous punctiform mutation in exon 9 of *KIT* (C>T): Pro456Ser and a nonsense mutation in exon 18 of *PDGFRA* were found in two different cases of pediatric GISTs. This is a different model from that observed in adult sporadic GISTs, where *KIT* mutations are ten times as common as *PDGFRA* mutations.

59.1.4.1 KIT and PDGFRA

As mentioned before, the main initial event in GIST tumorigenesis are often gain-of-function mutations in *KIT* or *PDGFRA* genes, located on the long arm of chromosome 4 (4q12) (◘ Figs. 59.5 and 59.6).

- In GIST, the most common mutations are found in *KIT exon 11* (60–70%) that affects the juxtamembrane domain (Corless et al., 2011). The most frequent types of mutation are in-frame deletions, followed by single nucleotide substitution, resulting in constitutive activity of the kit receptor. Approximately 80% of exon 11-mutated tumors are located in the stomach and typically show more spindled than epithelioid histology.
- Mutations in *KIT exon 9* are the second most common following the exon 11 mutations. Account for 8–10% of GISTs, affecting the extracellular domain

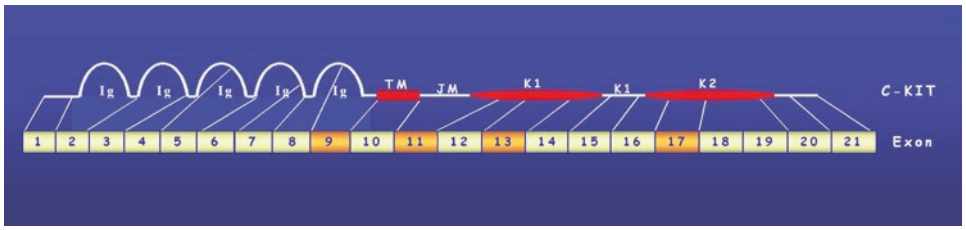


Fig. 59.5 C-KIT oncogene gene structure. The members of type III tyrosine kinase receptor family consist of a ligand-binding extracellular domain of 5 immunoglobulin (Ig) regions, an autoinhibitory intracellular juxtamembrane domain, and a kinase domain of an amino terminal ATP-binding region (activation loop)

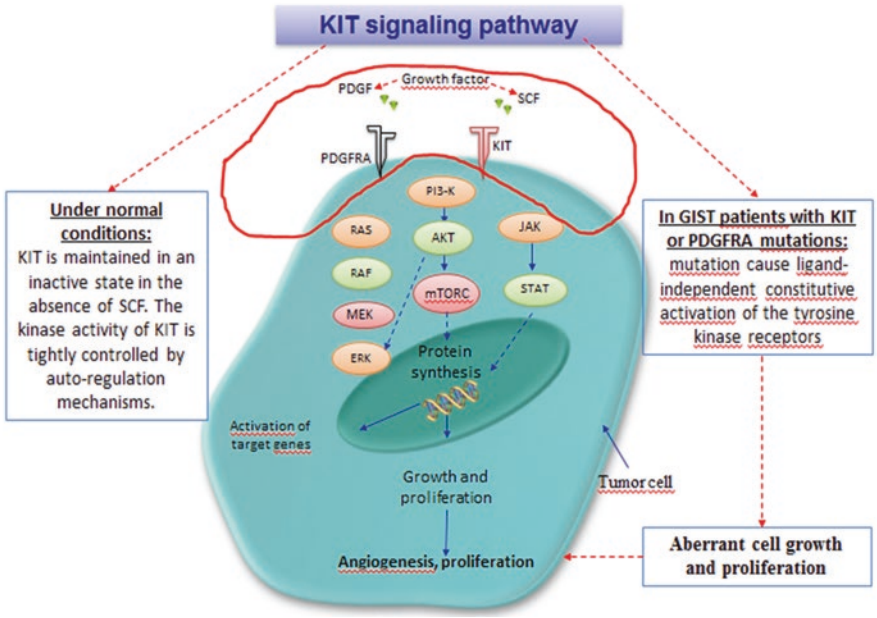
Fig. 59.6 KIT and PFGFRA signaling pathways

KIT and PDGFRA genes encode transmembrane glycoprotein receptor tyrosine kinase **(RTK).**

The **ligands** of KIT and PDGFRA are stem cell factor **(SCF)** and platelet-derived growth factor **(PDGF),** respectively.

Binding to the receptors results in **kinase activation**, initiating downstream signaling pathways, mainly through phosphoinositide 3-kinase (PI3K)/AKT, RAS/RAF/mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) pathways, that promote cell **proliferation** and **survival**. PMID: 24267995

Mutations in the **KIT or PDGFRA genes** may result in expression of a protein with constitutive RTK activity and **aberrant cell growth and proliferation.** (Fig 1.6)



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and 95% are duplications of codons 502 and 503 (Lux et al., 2000). These tumors have a higher prevalence in the small or large bowel.

Generally uncommon are the mutations is in *exons 13 and 17* of KIT (Corless et al., 2011).

- About 10% of GISTs harbor *PDGFRA mutations* (Heinrich et al., 2003b; Hirota et al., 2003). PDGFRA and KIT mutations are mutually exclusive. The majority of PDGFRA-mutated GISTs occur in the stomach, usually with epithelioid or mixed epithelioid and spindle cell histology. Although the activated pathways downstream are identical to KIT mutations, PDGFRA-mutated GISTs tend to have a lower risk of recurrence, and among metastatic GISTs, only 2.1% showed PDGFRA mutation compared with 82.8% in those with KIT mutations.

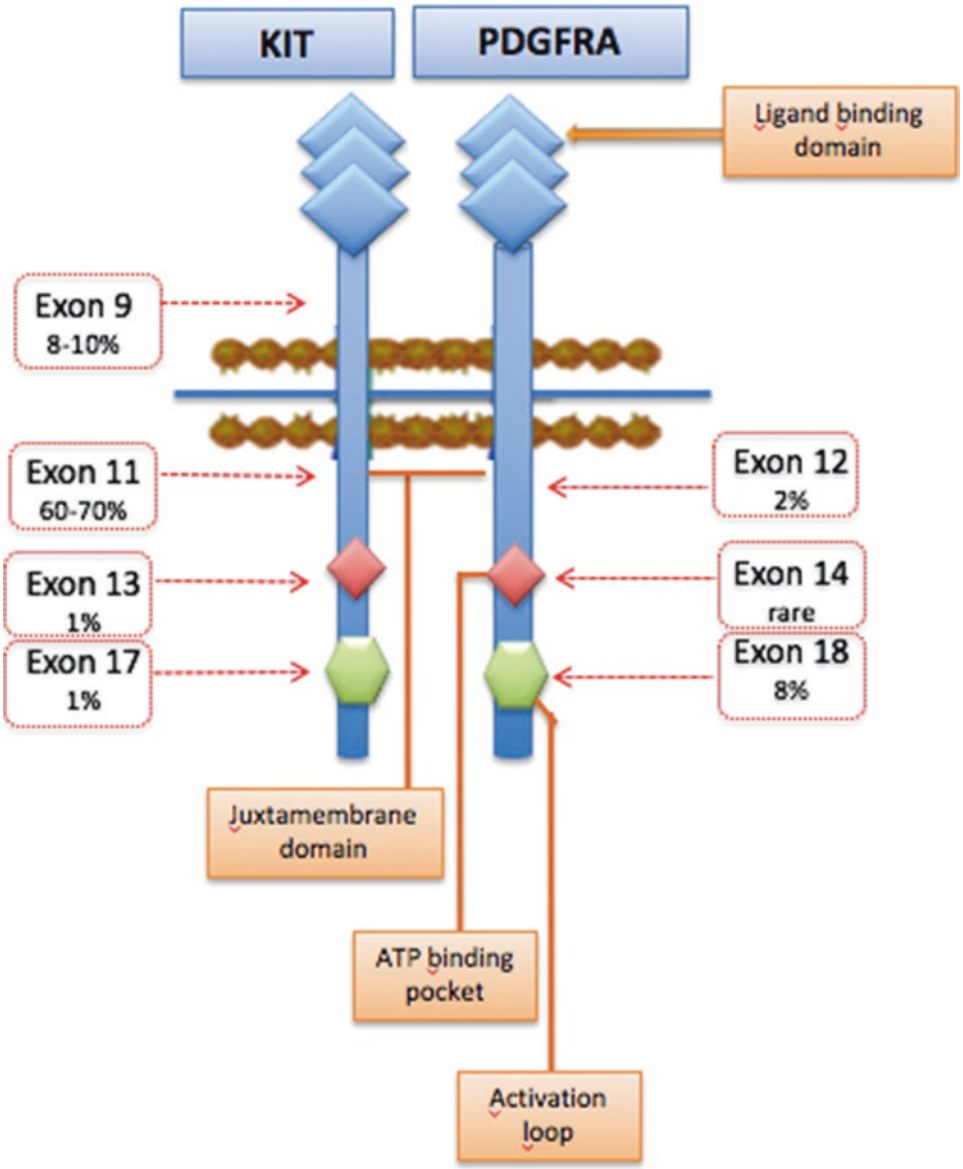


Fig. 59.7 Location and frequency of KIT and PDGFRA mutations

PDGFRA-mutated GISTs showed a variability of response to medical treatment. Most PDGFRA mutations in GISTs have been identified in *exon 18*: the most frequent mutation, *D842V*, represents 70% of PDGFRA mutations and 5% of metastatic GISTs and is the most common cause of primary resistance to therapy. The second most frequent mutation of exon 18, instead, the *deletion of codons 842 to 845*, confers imatinib sensitivity [14, 15] (Fig. 59.7).

59.1.5 Clinical Features

Unlike gastrointestinal carcinoma that has epithelial origin, GISTs are tumors of ► connective tissue, and therefore, most commonly grow extrinsically from the wall of GI tract. For this submucosal location, the GISTs achieve usually a large size without causing gastrointestinal obstruction or other symptoms typical of epithelial cancers (Fig. 59.8).

The *clinical presentation* of GIST is not characteristic and depends on the localization and the size of the tumor.

In contrast with epithelial carcinoma of the GI tract, which has an irregular mucosal or polypoidal growth with or without intestinal obstruction, GIST has a predominant *exophytic component* and displaces rather than invades the surrounding structures.

The GISTs *tumor size* at the time of diagnosis varies widely, from small nodules <2 cm to large masses, up to 30 cm in size (Corless et al., 2002).

The small tumors are, frequently, *asymptomatic* or associated with *nonspecific symptoms* and often diag-

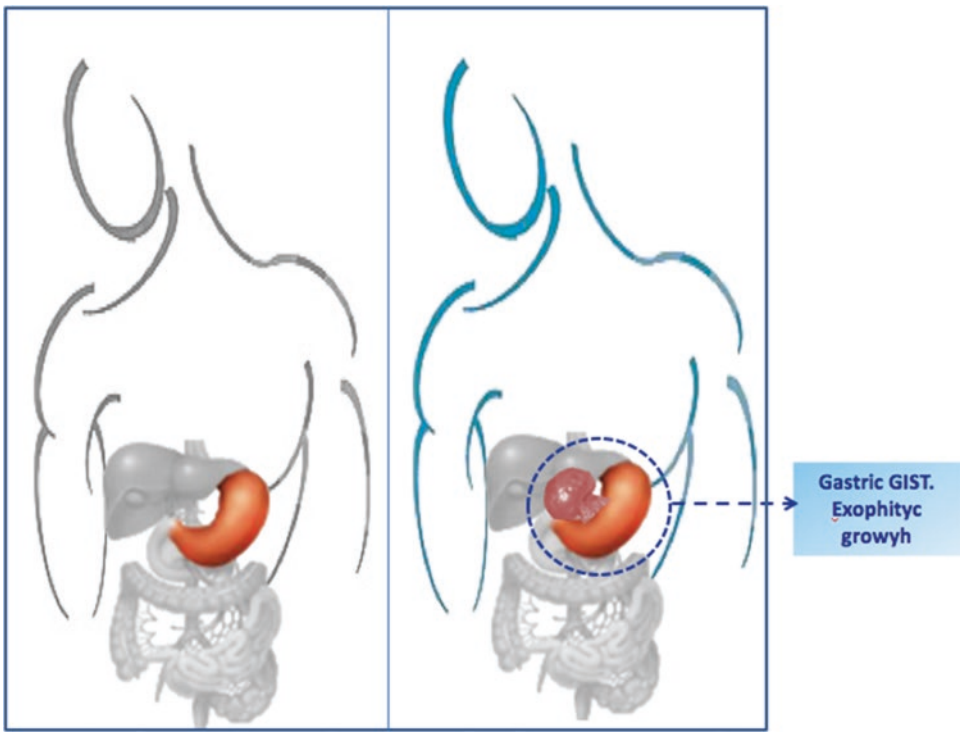


Fig. 59.8 Pattern of growth

nosed incidentally during endoscopic/surgical procedures or during radiologic studies performed to investigate manifestations of gastrointestinal tract disease.

Also for the voluminous tumors, the *symptoms* associated with GISTs are nonspecific and can include the following:

- Abdominal pain
- Nausea and early satiety
- Vomiting
- Anorexia and Weight loss
- Epigastric fullness

Localization of the tumor	Several clinical symptoms depending on localization of the tumor: for example, the esophageal tumors are present with dysphagia, odynophagia, retrosternal pain, and hematemesis; gastric tumors may cause epigastric pain, anorexia, nausea, vomiting, and weight loss
Obstruction	GISTs may also produce site-specific symptoms secondary to obstruction, for intraluminal growth of the tumors or for exophytic luminal compression (e.g., constipation in colorectal GIST or obstructive jaundice in duodenal GISTs)
GI bleeding	It can be produced by pressure and ulceration of the overlying mucosa with resultant blood loss and fatigue

In loss frequent cases, especially for large GISTs, the *GIST rupture* can occur into the abdominal cavity with life-threatening intraperitoneal hemorrhage [17].

59.1.6 Diagnosis

The diagnostic evaluation of gastrointestinal stromal tumors is based on imaging techniques, but the most important diagnostic tools remain the histology with the immunohistochemical examinations.

Small, asymptomatic lesions are usually discovered accidentally during endoscopy, ultrasonography, or computer tomography performed for other indications.

Endoscopy	Usually describes GIST as submucosal changes, in the majority of cases as oval protrusion, observed through the gastrointestinal lumen, with a covering mucosa often intact
Computed tomography	Shows these lesions as a solid mass with exophytic growth from the muscularis propria that displays contrast enhancement and may contain areas of necrosis (Fig. 59.9)
Endoscopic ultrasonography (EUS)	Besides endoscopy and computer tomography, it plays an important role in the diagnostic work-up of GISTs. Frequently, EUS shows GIST as hypoechogenic mass originating from different layers of the gastrointestinal tract wall, usually from the muscularis propria and muscularis mucosa, with an irregular outer margin and nonhomogeneous echo pattern

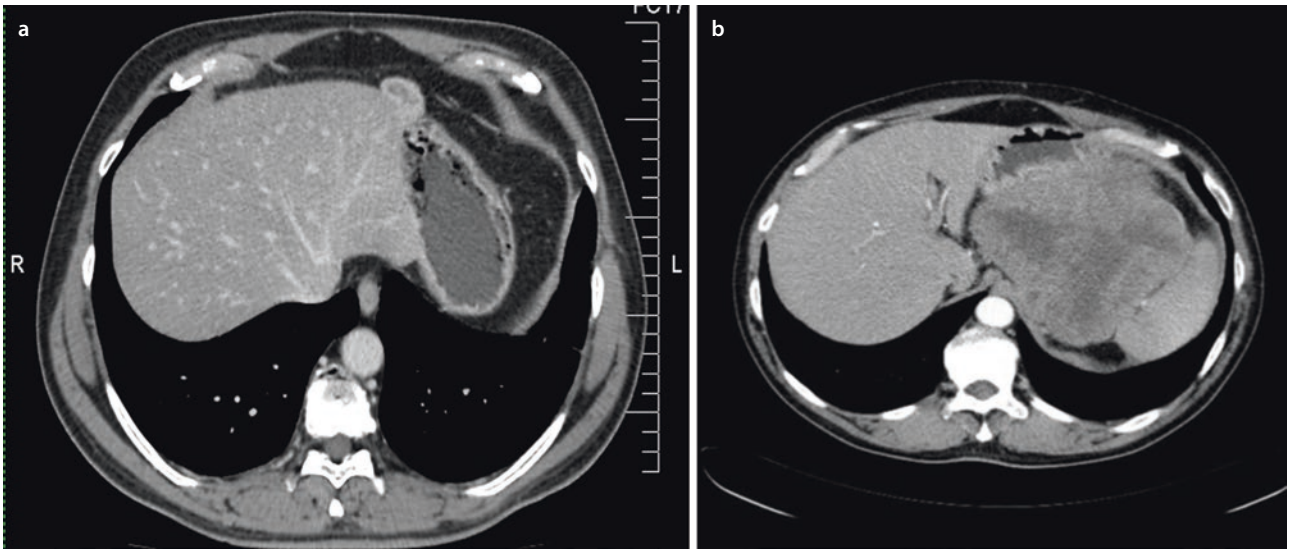
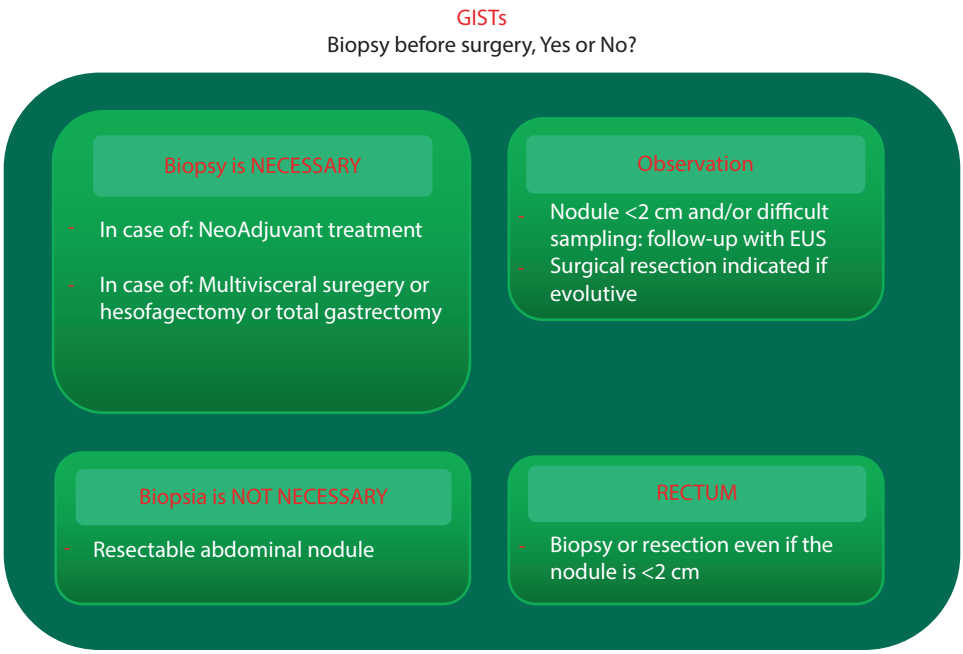


Fig. 59.9 **a** Small Gastric GIST. **b** Heterogeneously enhancing mass in the stomach, with necrosis

Magnetic resonance imaging (MRI)	May be an alternative to abdominal and pelvic CT scan. For rectal GISTs, MRI provides better preoperative staging information.

The final diagnosis is established on the basis of *histological examination of biopsy* with *immunohistochemical investigations.*



The evaluation of fluorodeoxyglucose (FDG) uptake using an FDG-positron emission tomography *(PET) scan*, or FDG-PET–CT, is useful mainly for early detection of the tumor response to molecular-targeted therapy [3, 17] (Fig. 59.10).

59.1.7 Prognostic Factors

Current ESMO guidelines do not recommend the use of TNM system for the classification and staging of GIST, due to the limitations of this system.

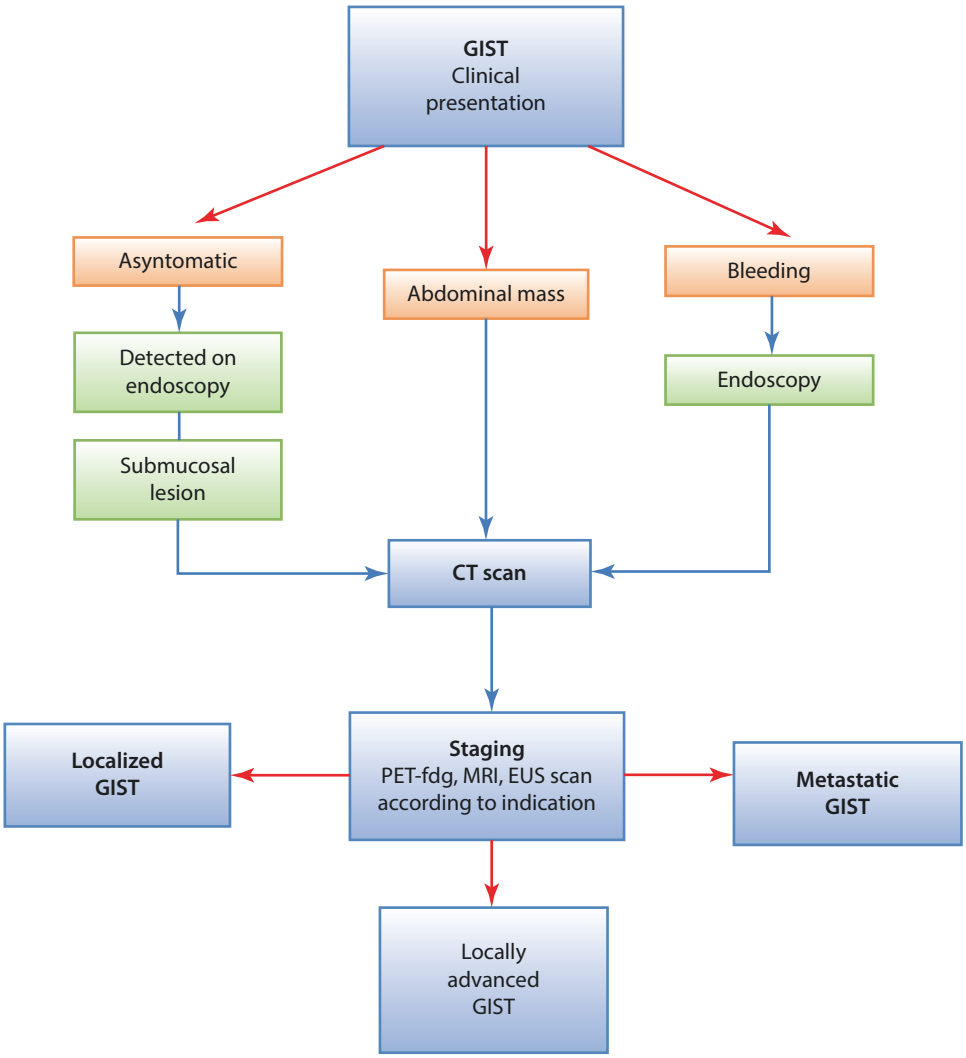


Fig. 59.10 Diagnostic evaluation of GIST. CT: computerized tomography; PET: positron emission tomography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound

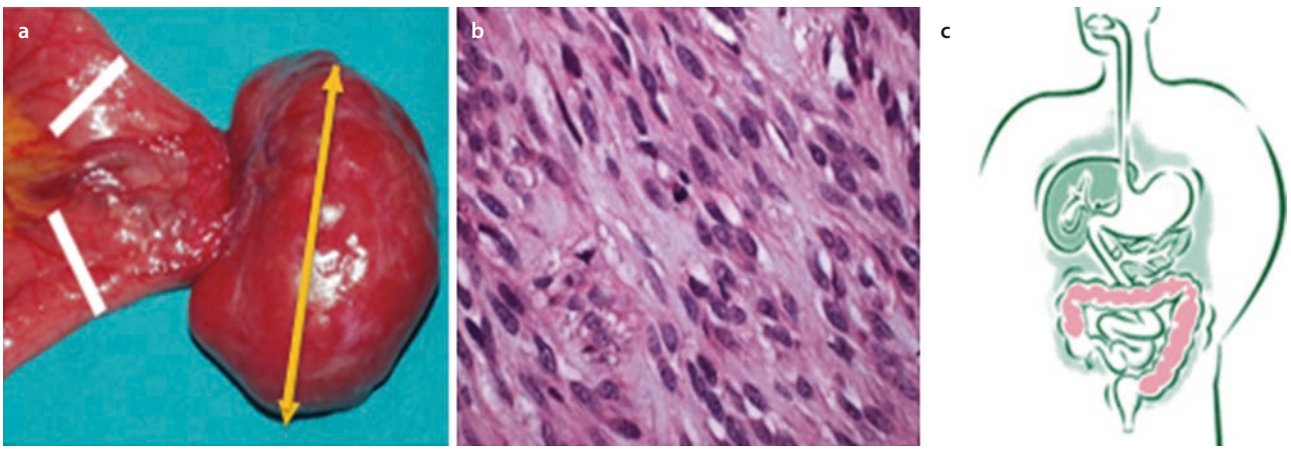


Fig. 59.11 Prognostic factors **a** tumor size; **b** mitotic activity; **c** anatomic site

Prognostic factors used for risk assessment affect the primary tumor site (Fig. 59.11):

- *Mitotic index*
- *Tumor size*
- *Tumor site: gastric* GISTs have a better prognosis than *small bowel or rectal* GISTs.
- *Tumor rupture* is an additional adverse prognostic factor.

This version of the risk assessment scheme is based on several large series published by Mietinnen and colleagues (2006) (Fig. 59.12), after integrated by Joensuu (Fig. 59.13).

More recently, prognostic heat and contour maps have been developed which should address issues associated with the nonlinear continuous variables of tumor size, mitotic index, and tumor rupture (Fig. 59.12).

Fig. 59.12 Joensuu's risk stratification for gastrointestinal stromal tumors

Risk category	Tumor size (cm)	Mitotic index (5 HPF)	Primary tumor site
Very low-risk	>2	<5	Any
Low-risk	2.1-5	<5	Any
Intermediate-risk	<5 5-10	6-10 <5	Gastric Gastric
High-risk	Any >10 Any >5 5.1-10	Any Any >10 >5 >5 >5	Tumor rupure Any Any Any Non-gastric Non-gastric

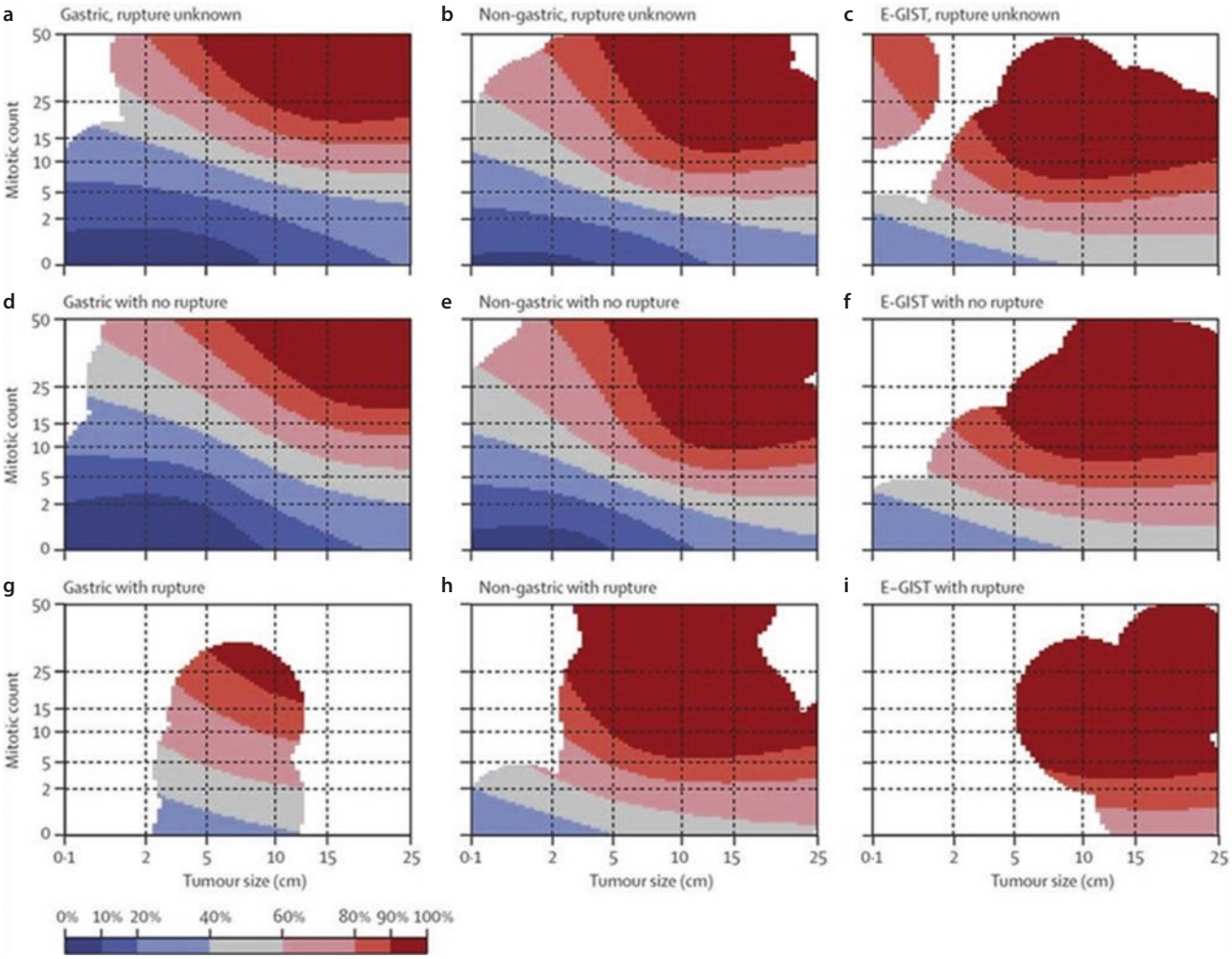


Fig. 59.13 Prognostic heat map for the risk assessment

In the future, also the *molecular profiling* of GISTs should be considered in risk classification systems. For example, GIST with exon 11 mutation has a higher risk of relapse than GIST WT.

Tumor mutational status is particularly important in GIST because it is predictive of response to TKI treatment, but has also a prognostic value: the type of mutation affects prognosis in metastatic disease. Patients with advanced GISTs and *KIT exon 11 mutation* have the superior prognosis and the longest progression-free survival (PFS) compared with *exon 9 mutations* or patients lacking both KIT and PDGFRA, who have less favorable PFS [15].

59.1.8 GIST Management

Prior to the advent of the tyrosine kinase inhibitors (TKIs), there were few treatment options available to patients with advanced GIST; the response rate to conventional chemotherapy agents was extremely low and the survival generally measured in few months [16].

Advances in understanding the molecular background of GIST allow the identification of abnormal receptor tyrosine kinase (RTK) signaling and the development of specific TKI, such as the first approved imatinib, that has become a paradigm for molecularly targeted therapies in solid tumors [17].

59.1.8.1 Focus on Imatinib (◘ Fig. 59.14)

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59.1.9 The Medical Treatment

59.1.9.1 Advanced and Metastatic GIST

In locally advanced inoperable and metastatic GIST patients, imatinib is the standard first-line treatment. The standard dose of imatinib is 400 mg daily. A higher dosage (800 mg/day) demonstrated a PFS advantage for KIT exon 9-mutated GISTs, despite no difference in overall survival (OS) and is endorsed by the NCCN, ESMO, and AIOM guidelines.

Treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression.
Imatinib achieved disease control in 70–85% of patients, but, despite the high response rate, the median time to progression (TTP) is approximately 24 to 30 months.
Median OS is approximately 57–60 months
5–23% of patients show a durable response lasting for more than 10 years.
10–15% of patients show progressive disease to imatinib within 3/6 months of starting therapy (primary resistance) and show stronger correlation with certain genotypes. These tumors most commonly are those with mutations in PDGFRA, particularly the D842V mutation in exon 18, or those lacking mutations in either KIT or PDGFRA.

- Despite the high efficacy of imatinib, virtually all metastatic GISTs will become resistant due to additional acquired mutation in KIT.

Secondary or acquired resistance to imatinib, it develops in the large proportion of patients who demonstrate disease control and ultimately develop progressive disease, usually within 2–3 years [18].

59.1.9.2 Molecular Profile of Primary and Secondary Resistance

The **primary resistance** arises in GSTs with no identifiable KIT or PDGFRA mutations is likely due to different mechanisms causing the disease development and activation of alternative signaling pathways. Therefore, treatment of these GISTs with the targeted agents other than imatinib, such as VEGFR, BRAF or MEK inhibitors, might be a better clinical alternative (Janeway et al, 2009)

In 1996, Druker and colleagues published their identification of a small molecule TKI, now known as imatinib, that can *selectively block the ABL kinase activity and induce cell death of BCR-ABL positive chronic myeloid lymphoma (CML) cells* (Druker et al, 1996).

Concurrently imatinib was shown **not only specific to BCR-ABL,** but *also blocks the enzymatic activity of the trasnmembrane receptor tyrosine kinases KIT and PDGFRA.* (Buchdunger, 2000; Heinrich, 2000a)

Imatinib binds to the ATP-binding site located in the amino-terminal lobe of the kinase domain that **competitively blocks ATP binding and consequent phosphorylation of KIT** (fig. 1.11).

Inhibition of mutant receptor KIT by imatnib led to GIST cell growth arrest and apoptosis (Tuveson, 2001).

Therafter, clinical development of imatinib for GIST therapy repidly progressed and has been considered the **standard first-line therapy** *for inoperable or metastatic GISTs since its approval in 2002.*

IN 2008, FDA approved ***adjuvant use of imatinib*** for patients with high risk of recurrence.

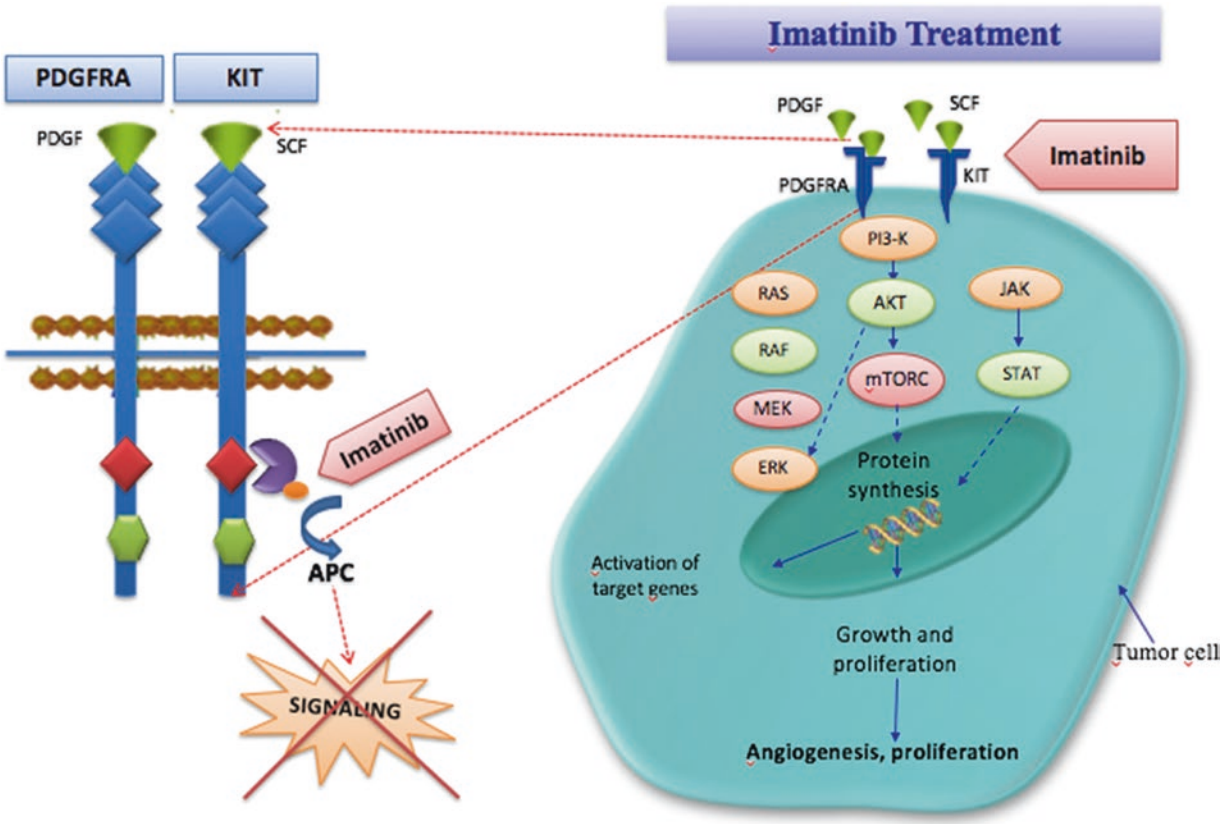
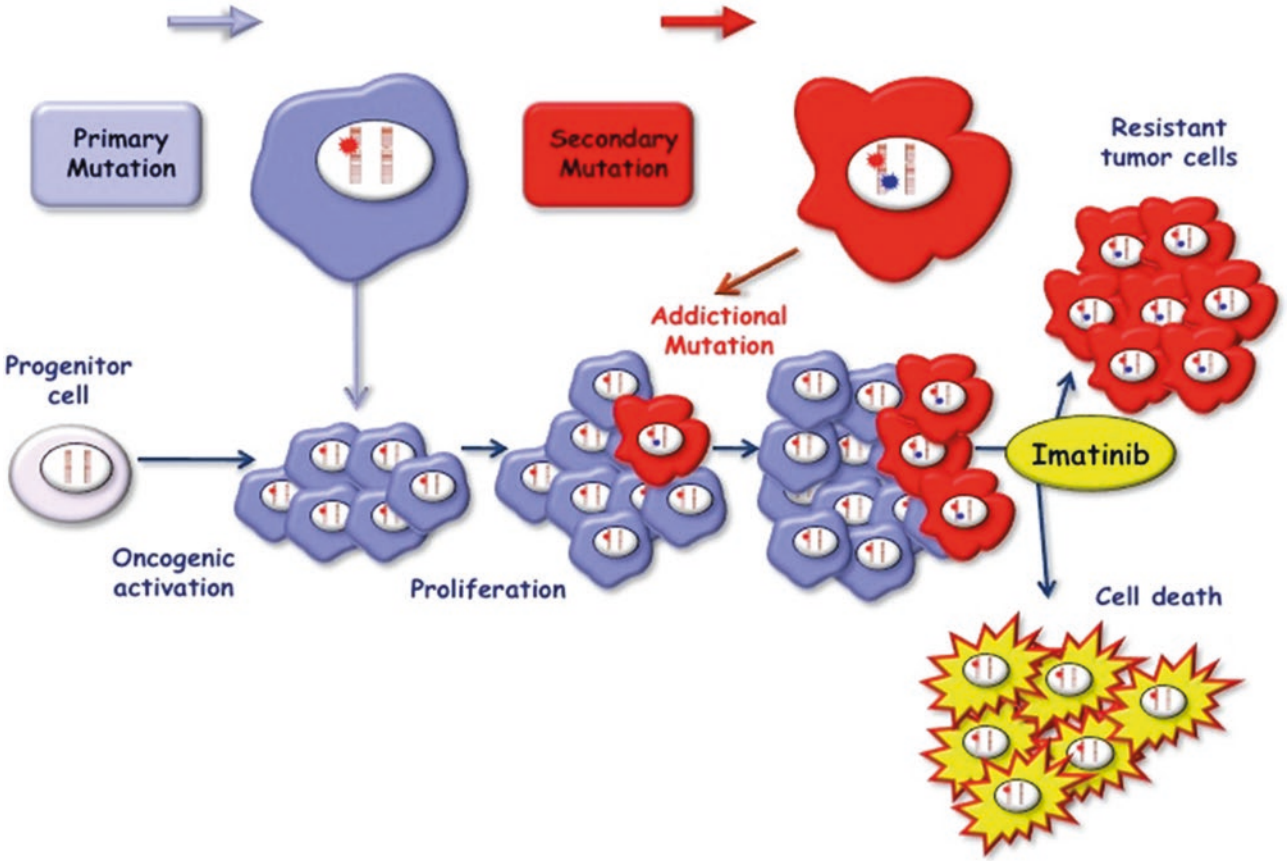


Fig. 59.14 Mechanism of action of imatinib

- Mutations in *exon 9* affect the extracellular KIT domain, mimicking the conformation change when SCF binds to the receptor, which induces higher degree of dimerization (Yuzawa et al., 2007). Since this mutation does not interfere with the kinase domain, exon 9 mutated KIT has the kinase domain same as the wild-type KIT, in which decreased sensitivity to imatinib was observed in vitro compared to exon 11 mutant KIT (Corless et al., 2011). Dose escalation is suggested for treatment of GISTs harboring these mutations (MetaGIST, 2010).
- Both clinical and in vitro studies have reported that *PDGFRA D842V mutation* is strongly resistant to imatinib (Corless et al., 2005; Heinrich et al., 2008a; Weisberg et al., 2006). This mutation results in a change in the kinase activation loop that strongly favors the active conformation of the kinase domain, which consequently disfavors imatinib binding (Gajiwala et al., 2009; Heinrich et al., 2003a). Patients with D842V-mutant GISTs show low response rates and short progression-free and overall survival during imatinib treatment (Biron et al., 2010).
- In addition to mutations, *gene amplification of KIT or PDGFRA* was shown as a potential mechanism leading to either primary or secondary resistance (Debiec-Rychter et al., 2005; Liegl et al., 2008; Miselli et al., 2007).



Secondary mutations is the main known mechanism for deveoping imatinib acquired resistance (Antonescu et al, 2005; Grimpen et al, 2005; Heinrich et al. 2006).
The most common mechanism is the occurrence of secondary mutations in the same gane that was originally activated and that render these clones resistant to imatinib (clonal evolution).
The most common secondary mutations occur in the ATP-binding pocket (encoded by exon 13 and 14) and in the kinase activation loop (encoded by exons 17 and 18).

59.1.9.3 Type of Progression

Most of the imatinib-resistant tumors exhibit inter- and intratumor heterogeneity (Liegl et al., 2008; Loughrey et al., 2006; Wardelmann et al., 2006): different types of secondary mutations across the multiple nodules of the same patient, and in different areas of the same tumor, cause the onset of resistant subclones.

This heterogeneity has important implications onto the efficacy of second-line TKI therapy after the first-line imatinib treatment.

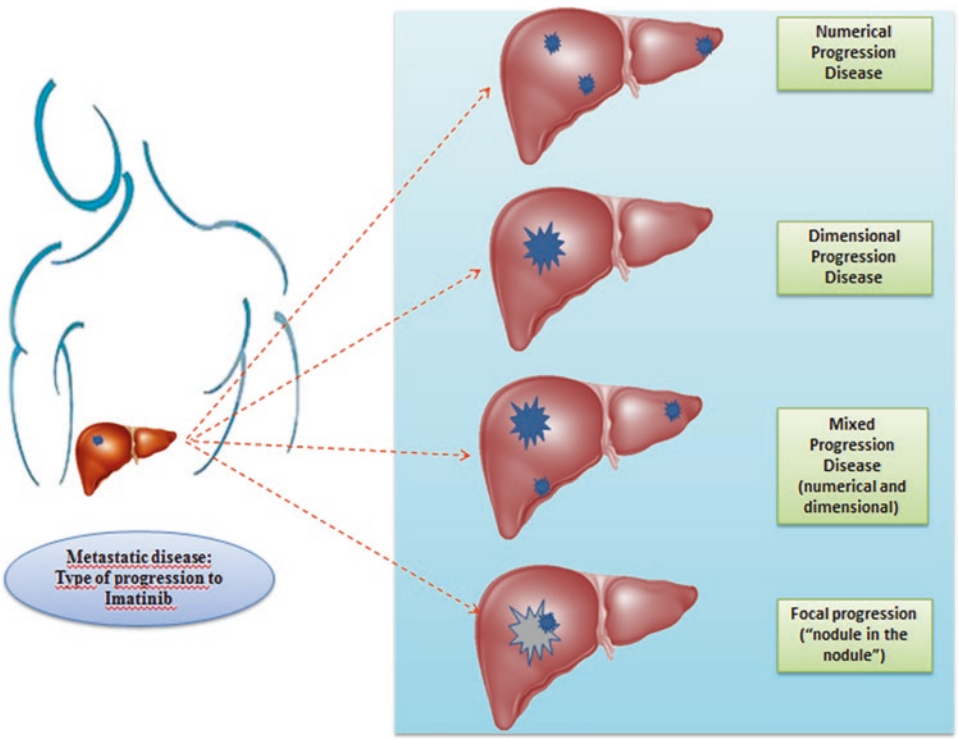
The type of progression disease (PD) evaluated with CT scan can be distinguished into different groups:

- *Dimensional PD*: characterized exclusively by dimensional growth of pre-existing lesions
- *Numerical PD*: characterized by the occurrence of new lesions
- *Mixed PD*: characterized by both dimensional and numerical PD
- Exists also a "focal progression" into a lesion in previous response to the treatment, the so-called nodule in the nodule (◘ Fig. 59.15)

59.1.9.4 Strategies to Overcome the Resistance

- *Second-line treatment*
  For GIST patients who progress on the standard dose of imatinib (400 mg daily), both imatinib dose escalation (800 mg daly) and sunitinib are feasible options.
- *Imatinib 800* mg daily should be considered for patients who was started on first-line imatinib 400 mg daily and experienced disease progression, on the basis of two large dose finding randomized phase III trials 14–15.
- *Sunitinib*, an oral multitarget tyrosine kinase inhibitor with high selectivity for KIT and PDGFRα, is an alternative strategy to overcome resistance for imatinib-refractory patients. In a randomized phase III trial, sunitinib 50 mg 4 weeks on and 2 off improved significantly PFS over placebo in second-line setting for those patients who had progression to first-line imatinib 17. However, sunitinib 37.5 mg continuously seems to be similarly effective and safe to sunitinib standard dose.
  The degree of disease control, including length of PFS and median OS, is significantly higher in patients whose GIST is with primary exon 9 mutation in KIT or those with no mutations in either KIT or PDGFRA.
- *Third-line treatment*
  Regorafenib is a recent third-line standard of care for metastatic GISTs resistant to both imatinib and sunitinib [19].

  Besides KIT and PDGFRA, this TKI also inhibits VEGFR1–3, TEK, RET, RAF1, BRAF, and BRAFV600E and FGFR (Wilhelm et al., 2011). Similar to sunitinib, regorafenib delayed the progression of patients for only 3.9 months compared to the placebo treatment (Demetri et al., 2013).



◘ **Fig. 59.15** Type of progression to imatinib in metastatic disease

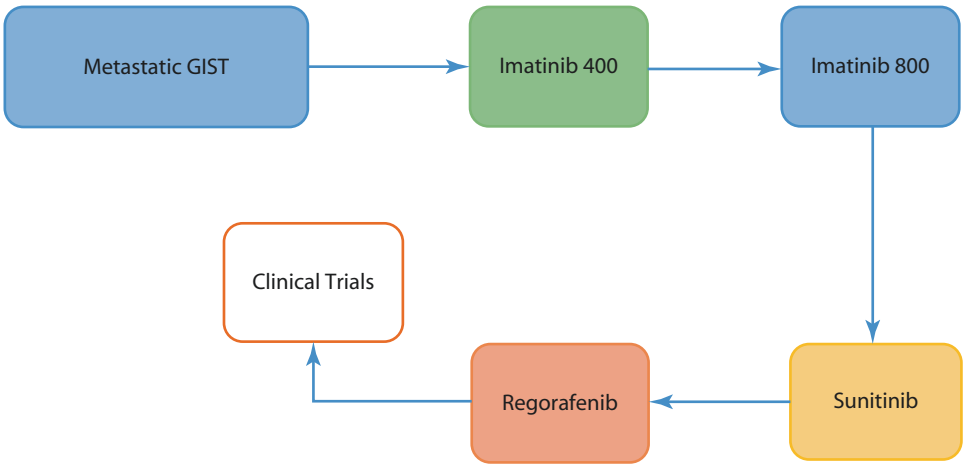


Fig. 59.16 Therapeutic algorithm for Metastatic GIST

For patients progressing to regorafenib, inclusion in clinical trials is indicated. In the absence of clinical trials, an option may be the treatment rechallenge with imatinib [20, 21] (Fig. 59.16).

59.1.9.5 New Therapeutic Targets and Treatments to Overcome Resistance to TKI

Several alternative TKI targeting KIT/PDGFRA (nilotinib, masatinib, sorafenib, dovitinib, pazopanib), multiple RTK (crizotinib, cabozantinib), or downstream signaling pathways (buparlisib, alpelisib, binimetinib) were studied in GIST patients with resistance to approved TKI.

Many clinical trials testing the compounds alone and in combination are ongoing, but unfortunately, none of these drugs has been registered for GIST treatment.

Novel agents, with an enhanced activity against specific secondary KIT/PDGFRA mutations, are currently being evaluated in preclinical and clinical settings [22].

Ponatinib	Multitarget inhibitor (PDGFRA, VEGFR2, FGFR1, and Src) approved for TKI-refractory leukemia. Potently inhibits KIT exon 11 primary mutants and a range of secondary mutants and has been shown to induce regression in engineered and GIST-derived tumor models containing these secondary mutations. Demonstrated a clinical benefit rate (CR, PR, or SD ≥16 weeks) of 55% in patients with primary KIT exon 11 mutation
Crenolanib	Inhibits the imatinib-resistant PDGFRA p.D842V-mutated kinase and also reduced the expression of KIT/PDGFRA by inhibiting MAPK and stabilizing ETS translocation variant 1 (ETV1) in mutated GIST. A phase III study is currently ongoing
BLU-285 (a vapritinib)	Highly selective inhibitor of KIT exon 17 mutations was also found to inhibit PDGFRA p.D842V mutant activity. Preliminary data from clinical trial showed a tumor reduction in all PDGFRA p.D842V-mutated patients
PLX9486 (Plexxikon)	Had an inhibitory effect on proliferation in a TKI-resistant PDX model (KIT exon 11 + 17), where its activity was more pronounced than imatinib. Currently, is evaluated alone and also in combination with pexidartinib
DCC-2618 (ripretibib)	Switch-control tyrosine kinase inhibitor active against a broad spectrum of KIT and PDGFRA mutations, under evaluation in clinical trials

59.1.9.6 Role of Medical Treatment in Localized Disease

Given the efficacy of imatinib in the metastatic setting, the use of imatinib has been extended to the *adjuvant setting* for the treatment of adult patients following GIST resection.

Risk stratification is essential to identify and better define the patients with GIST who are most likely to benefit from adjuvant imatinib therapy.

Three randomized phase III clinical trials have examined the use of imatinib 400 mg daily as an adjuvant for 1, 2, and 3 years; all three showed that it extends recurrence-free survival (RFS) in comparison with placebo or surveillance.

Additionally, the initial and long-term results provided by the AIO study demonstrated that 3 years of imatinib significantly improves RFS and OS compared with 1 year of therapy.

According to survival findings in the AIO trial, 3 years of adjuvant imatinib therapy are recommended for patients with GIST with high-risk features.

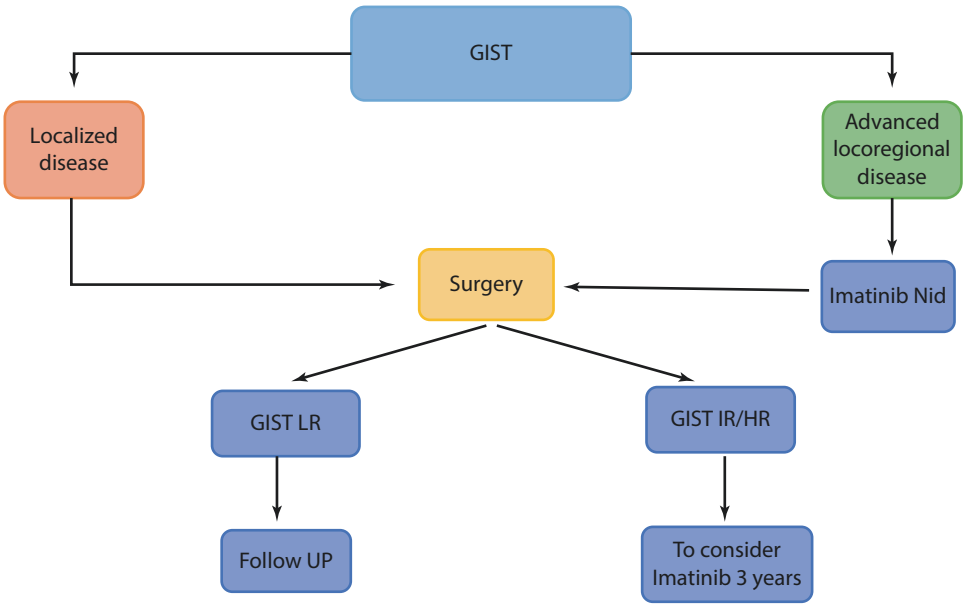


Fig. 59.17 Treatment strategy for GIST; LR: Low risk; IR: intermediate risk; HR: high risk; Njd:

Moreover, two randomized trials are ongoing in high-risk GIST patients: a Scandinavian study comparing 5 years with 3 years and a French study comparing 6 years to 3 years of imatinib.

The use of adjuvant imatinib is not recommended for low risk and very low risk, but there is no consensus for intermediate risk. In this situation, the risks and benefits of treatment should be shared with the patient.

In the *neoadjuvant setting,* its preoperative use is proposed in tumor bulk reduction in order to ease complete surgical resection or make organ preservation more likely in initially unresectable or borderline resectable disease. Imatinib should be continued for 6–9 months but not extended beyond 12 months because of the risk of imatinib resistance and of usually minor additional tumor shrinkage

If an adjuvant or neoadjuvant treatment is indicated, the mutational analysis is required to predict the response to treatment with imatinib [23, 24] (Fig. 59.17).

neoadjuvant

59.1.10 Response Evaluation

Response evaluation is complex, and early progression should be confirmed by an experienced team. Antitumor activity translates into tumor shrinkage in the majority of patients, but some patients may show changes only in tumor density on CT scan, or these changes may precede delayed tumor shrinkage. These changes in tumor radiological appearance should be considered as the tumor response. Even increase in the tumor size, in particular, may be indicative of the tumor response if the tumor density on CT scan is decreased. Even the "appearance" of new lesions may be due to their being more evident when becoming less dense [25].

Therefore, both tumor size and tumor density on CT scan, or consistent changes in MRI or contrast-enhanced ultrasound, should be considered as criteria for tumor response. An FDG-PET scan has proved to be highly sensitive in early assessment of tumor response and may be useful in cases where there is doubt, or when early prediction of the response is particularly useful (e.g., preoperative cytoreductive treatments) (Fig. 59.18).

A small proportion of GISTs have no FDG uptake, however. The absence of tumor progression at 6 months after months of treatment also amounts to a tumor response. On the other hand, tumor progression may not be accompanied by changes in the tumor size. In fact, some increase in the tumor density within tumor lesions may be indicative of tumor progression. A typical progression pattern is the "nodule within the mass," by which a portion of a responding lesion becomes hyperdense [24, 26].

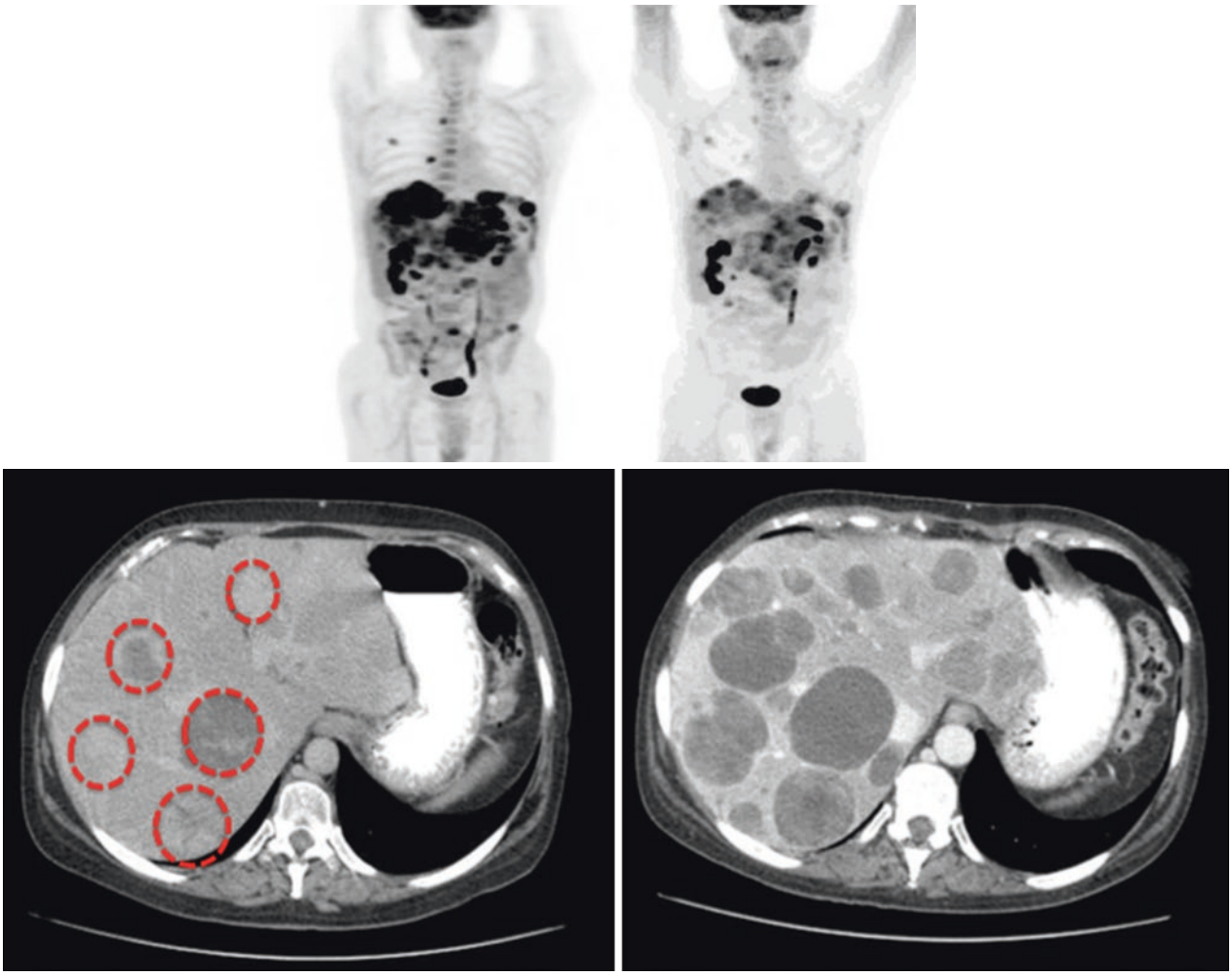
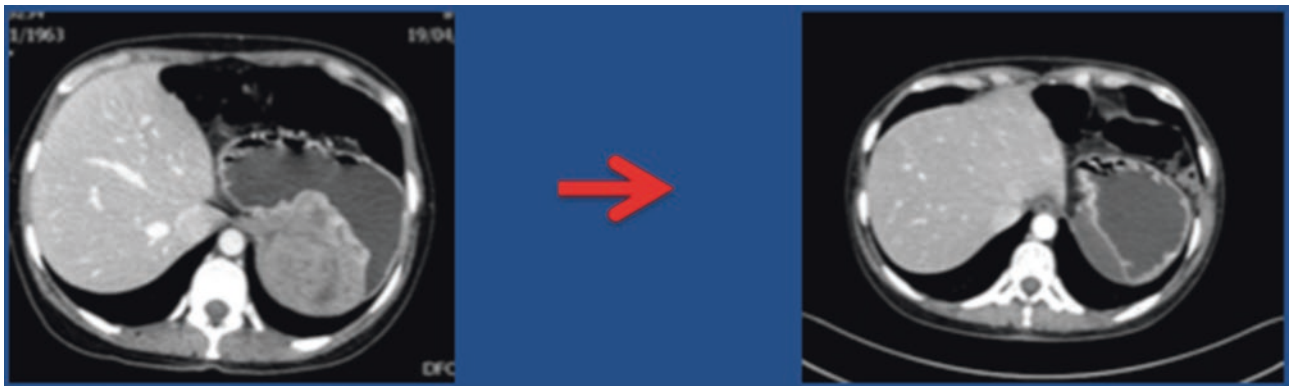
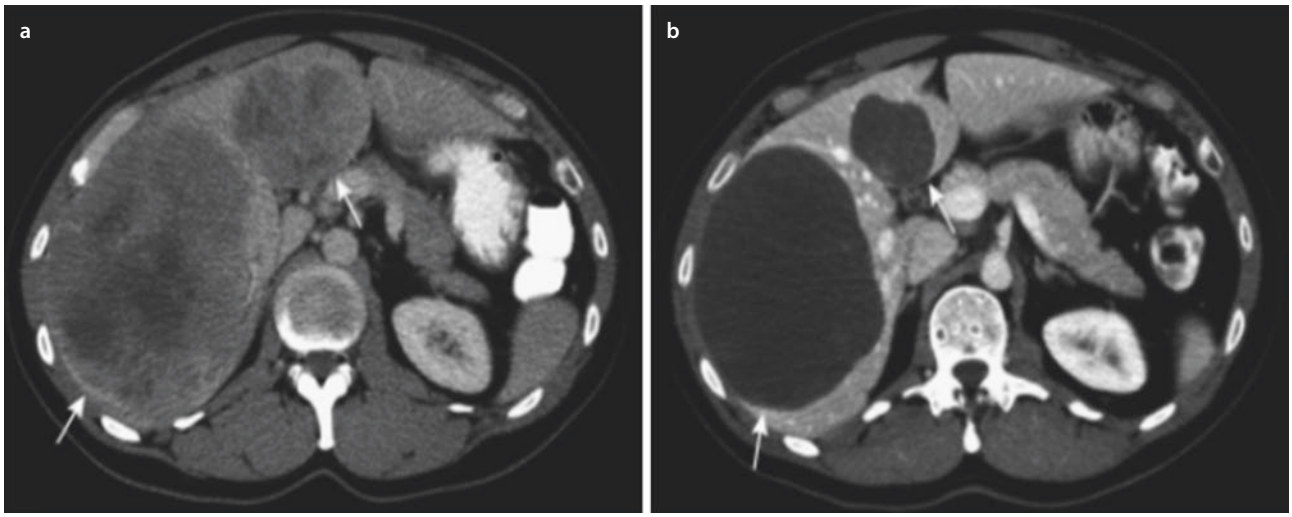


Fig. 59.18 Effect of imatinib therapy using positron emission tomography on fluorodeoxyglucose (FDG) levels: tumors that had a robust response to imatinib present a significant decrease in FDG signal, even within 24 hours of the first dose (Van den Abbeele & Badawi, 2002)

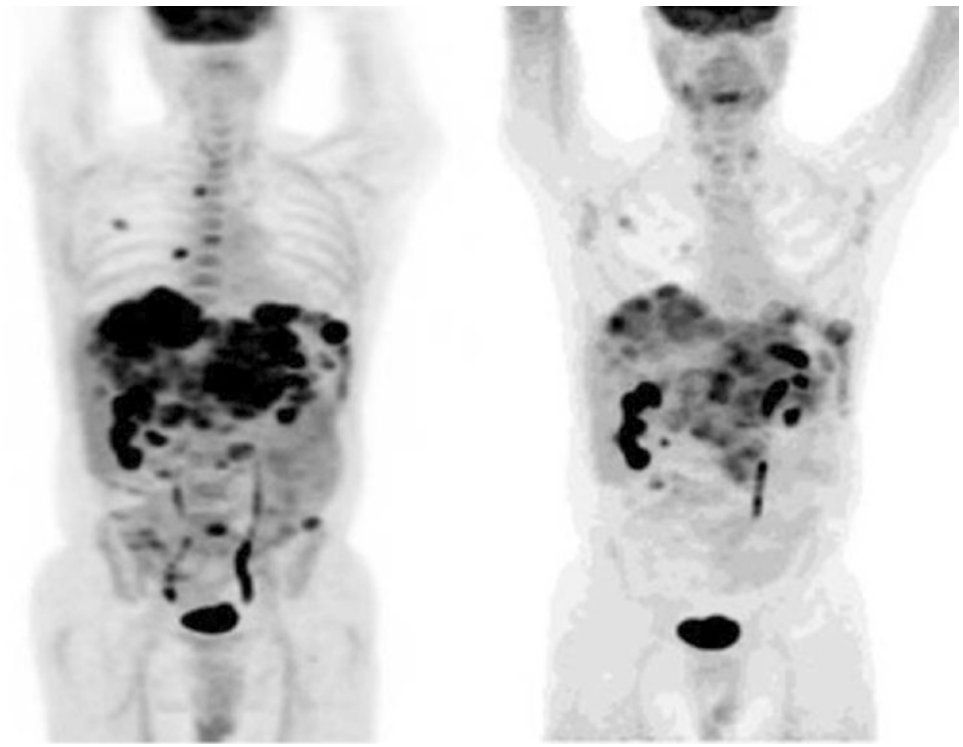


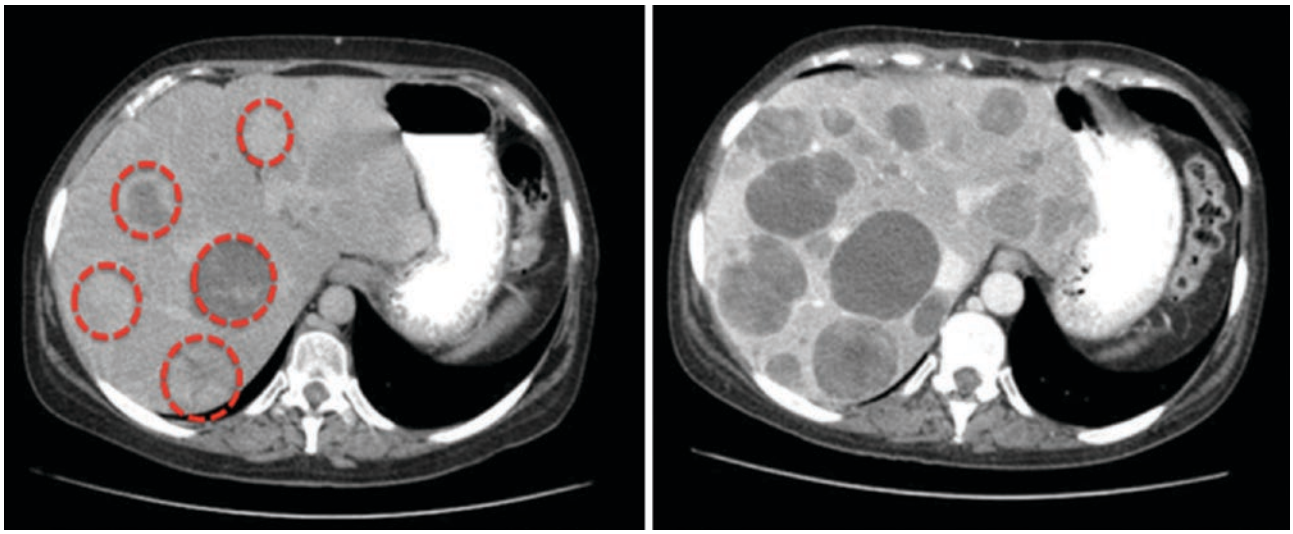
RECIST Response



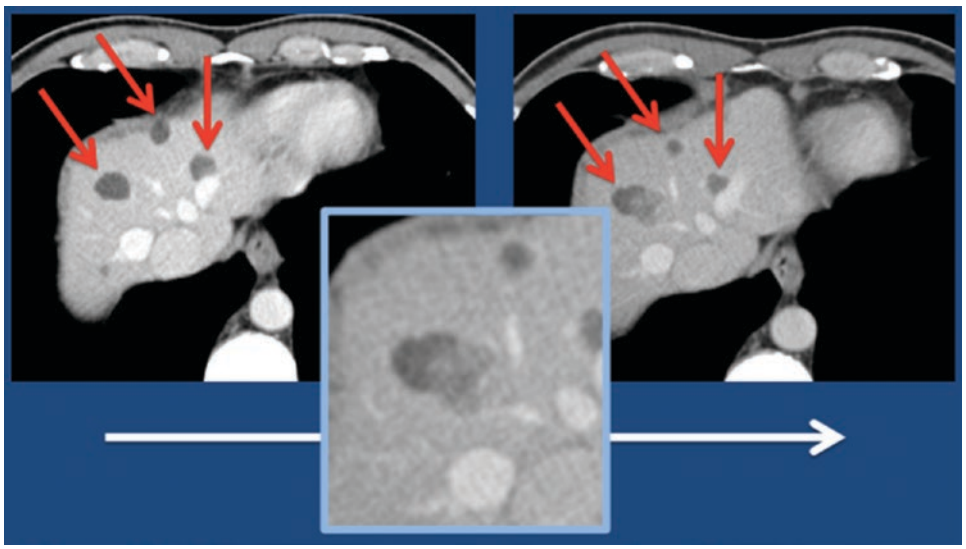
CHOI Response

Fig. 59.18 (continued)

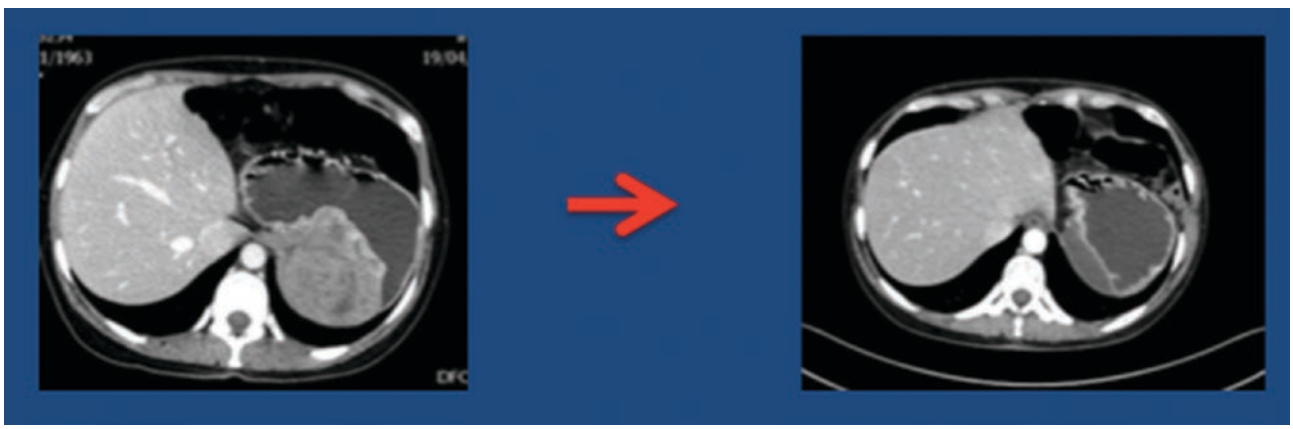




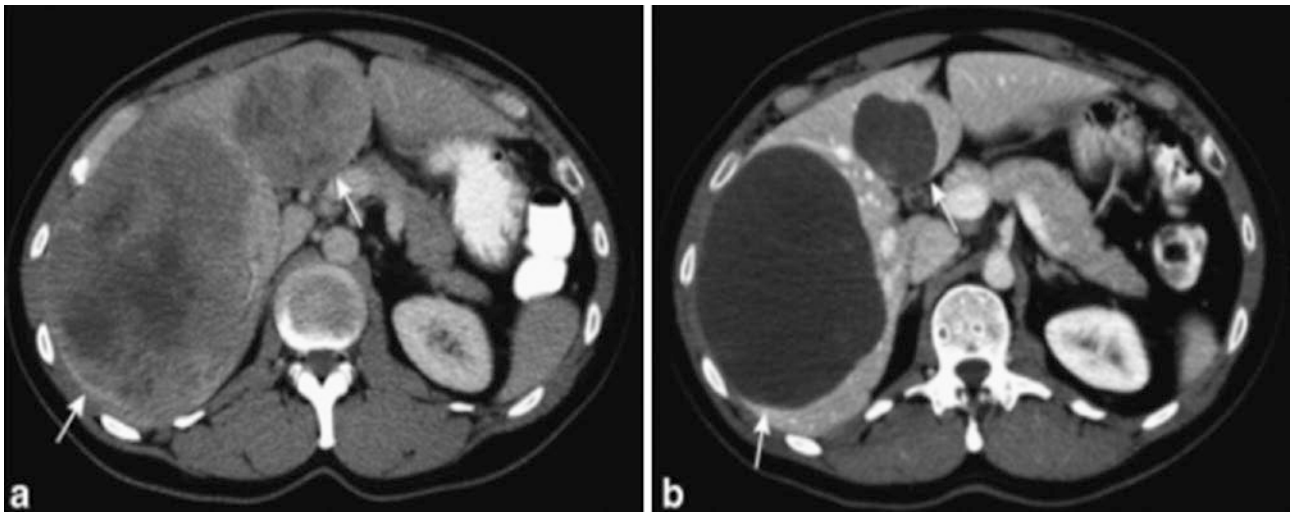
Pseudoprogression



Nodular Progression



RECIST Response



CHOI Response

59.2 The Role of Surgery in the Management of GIST

Sinziana Dumitra and Alessandro Gronchi

59.2.1 Introduction

While the management and ultimately survival of GIST was revolutionized at the dawn of the twenty-first century with the discovery of the *c-kit* tyrosine kinase mutations [27, 28] and that of targeted therapy [29], allowing disease control in a historically difficult to manage disease [30–36], surgical management remains the cornerstone of GISTs management and is based on the phase of disease at presentation. While a well-established and valid staging system is not currently in use for GIST, however a practical way to conceptualize this disease and its surgical management is to think of it as localized, locally advanced, or metastatic disease.

59.2.2 Localized GIST

Much of the surgical management of GIST truly depends on the primary site of disease occurrence; the most common site being stomach (50%), followed by small bowel (25%), and colon and rectum (10%) [37–41]. There are some reports of less common locations of GIST, namely, omentum, mesentery, and retroperitoneum [42]. The overall disease prognosis depends on size, location, mitotic count, and tumor rupture [43]. While the surgical options might differ based on location, the principles of an oncologic surgical resection remain the same. First of all, it is important to thoroughly inspect the abdomen to ensure absence of peritoneal metastases. Secondly, achieving negative resection margins over the organ of origin is recommended, even if a clear association between quality of surgical margins and disease free and overall survival has not been demonstrated [37], save for rectal GIST. This is mainly due to the variety of presentations, with the majority of GIST having an intra-abdominal growth. When the tumor is confined to the GI wall, quality of surgical margins is likely to be more critical. A main advantage in GIST is that compared to other sarcomas and adenocarcinomas margins need be less wide, allowing for less extensive and morbid surgery. Thirdly, surgeons should manipulate GISTS with great care as not to rupture these friable tumors. Lastly, given that these stromal tumors rarely metastasize to lymph nodes, a lymphadenectomy is not performed routinely unless the presence of suspicious nodes is detected preoperatively.

59.2.3 Gastric GIST

Adequate preoperative assessment includes imaging as well as upper endoscopy. In the stomach, GIST often presents as an exophytic mass that can be easily resected or wedged out with the aid of a stapler (Fig. 59.19, panel a). While the authors believe that all GISTs should be resected given the fact, some have argued for potential observation at smaller sizes (<2 cm) after discussion with the patient [44]. It is important to highlight that symptomatic GIST (e.g., bleeding, perforation, obstruction) should undergo resection. Emerging endoscopic techniques have also been successful in adequately

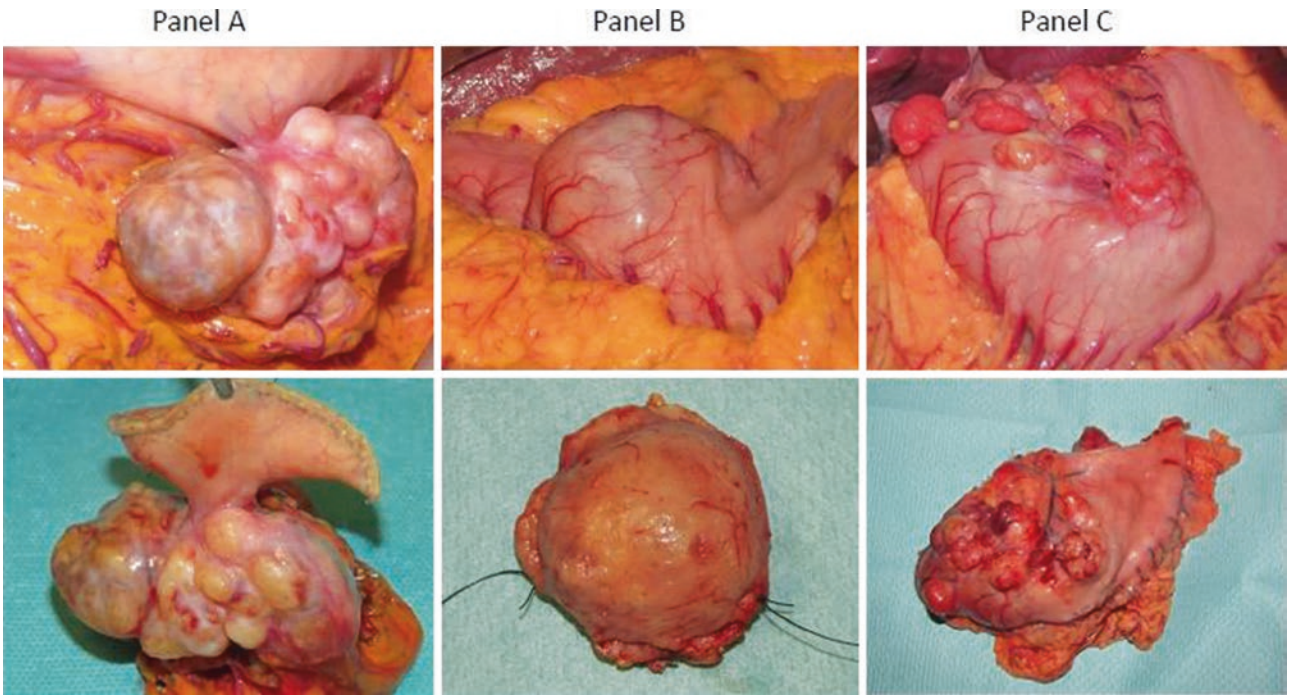


Fig. 59.19 Macroscopic appearance of gastric GIST and its implication for surgical management: extraluminal growth, which can be resected with a wedge mechanical suture in panel **a**; intraluminal growth, which can be resected conservatively with a wedge manual suture in panel **b**; multinodular growth, which can only be resected with a conventional subtotal/total gastrectomy in panel **c**

removing gastric small (i.e., <2 cm) GIST [45, 46]. These are particularly useful in patients with multiple comorbidities who could not undergo a surgical procedure or as an alternative to active surveillance.

If larger non-exophytic GISTs are encountered often times, a large resection can be avoided by simply incising the gastric wall and resecting the tumor with an adequate margin, under direct vision, and subsequently closing the gastric wall by approximating the edges (Fig. 59.19, panel b). This allows for a controlled gastric wedge, while avoiding resecting a large portion of the stomach. A particular case where great care needs to be taken when resecting a gastric GIST is one at or close to the gastroesophageal (GE) junction; a 32 French bougie should be utilized to ensure that the GE junction remains patent and sufficiently wide after wedge resection. These patients need to be carefully assessed in the preoperative setting and if a gastoesophageal resection would be necessary in order to obtain negative margins; then neoadjuvant targeted therapy should be considered in order to spare such an extensive resection and anastomosis. Very rarely is a subtotal or total gastrectomy required for GIST. Likewise multivisceral resections, including pancreas, spleen, and liver, are rarely required, as the tumor can often be separated from surrounding organs. However, when this is anticipated not to be the case, a preoperative therapy with imatinib should be considered, unless the tumor harbors an insensitive mutation, such as PDGFRA D842V, or belongs to the SDH-deficient subgroup, both insensitive to imatinib and all other approved TKIs. Finally, SDH-deficient GIST is predominantly located to the stomach and is multifocal (Fig. 59.19, panel c). As a result of this specific subgroup, subtotal/total gastrectomy is more often required, along with regional lymphadenectomy, as lymph node metastases are more common.

An important surgical modality to discuss is the utilization of laparoscopic surgery in GIST that allows for a faster recovery, shorter hospital stay, and decreased overall costs of care. Recent studies and meta-analyses did not identify oncologic outcome differences when using laparoscopic surgery when compared to open [47–49]. Even in studies assessing larger GIST >5 cm, oncologic results were similar [50]. The authors do caution in case of large tumors to ensure the extraction site is large enough and suggest the tumor be extracted in a specimen bag as to avoid rupture and spillage. Of note, imatinib therapy can be used to downsize the tumor and allow a laparoscopic procedure.

59.2.4 Duodenal GIST

The surgical management of duodenal GISTs can be more challenging and greatly depends on size as well as the portion of the duodenum affected. The most com-

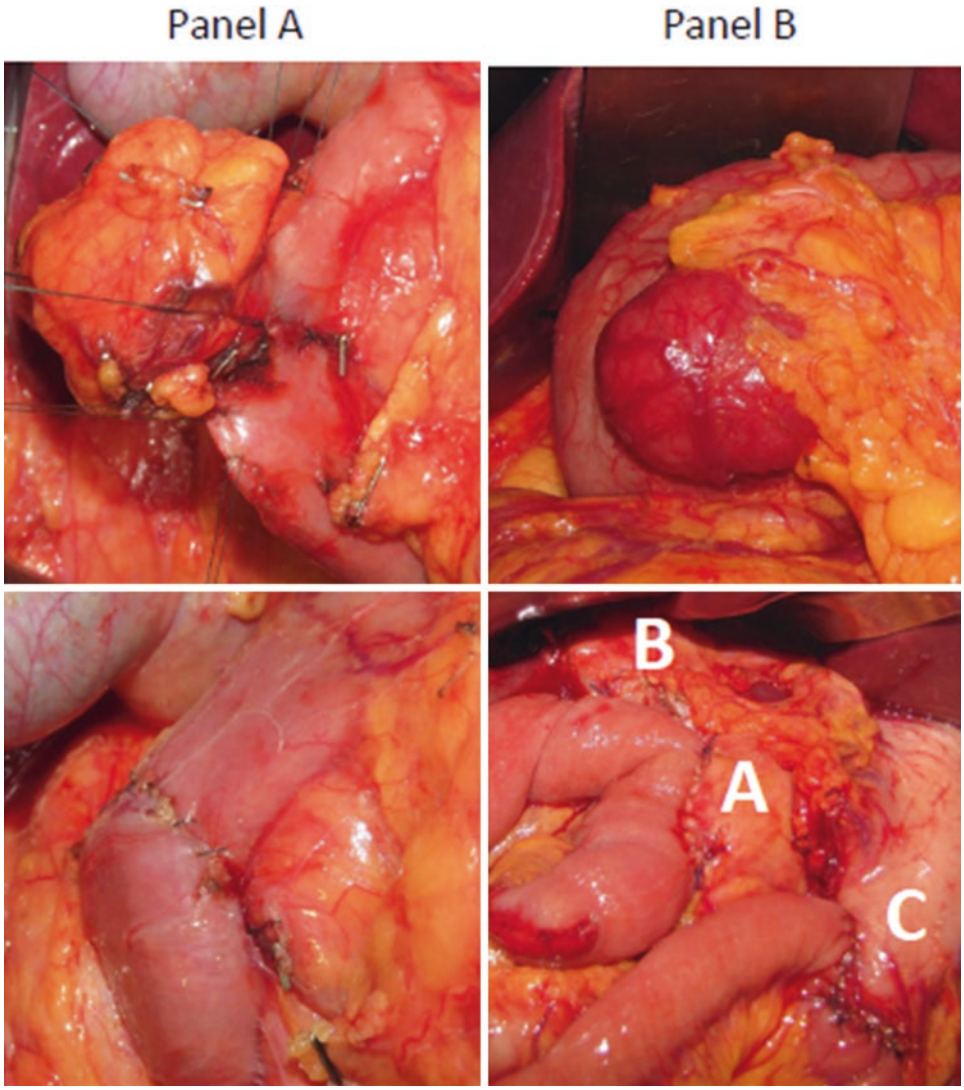


Fig. 59.20 Macroscopic appearance of a duodenal GIST occurring on the 2nd portion of the duodenum and its implication for surgical management: antimesenteric growth, which can be resected conservatively with a wedge manual primary suture (or at times with a jejunal loop interposition) in panel **a**; mesenteric growth, which can be resected only with a pancreaticoduodenectomy and a Whipple reconstruction (pancreatic [A], biliary [B] and gastrointestinal [C] anastomoses) in panel **b**

mon site of duodenal GIST occurrence is the second portion followed by the third, fourth, and finally the first portion of the duodenum [51, 52].

Another important limitation that might not allow for a local excision is whether the tumor occurs on the mesenteric or non-mesenteric side [52]. Given the risk of duodenal stricture, after an extensive Kocher maneuver, we suggest a wedge excision under direct vision and primary closure (Fig. 59.20, panel a). If necessary, the common bile duct can be identified by using a pediatric feeding tube. More specific reconstructions are mandated by the size of the defect and the location (Fig. 59.20, panel b).

As with GE junction tumors if they occur at the insertion of the bile duct in the D2 or D2-D3 area, for which a pancreaticoduodenectomy might be required to obtain an adequate negative margin excision, then neoadjuvant therapy is suggested in order to downsize the tumor and allow for a less morbid resection. In our experience, the extent of surgery does not confer a disease-free or survival advantage [53].

59.2.5 Small Bowel GIST

Small bowel GISTs can have widely varying presentations such as palpable masses, obstruction, bleeding, and rupture, and more increasingly often they present incidentally based on imaging or endoscopy. Their prognosis varies widely based on size and mitotic count [54]. Surgery upfront should be offered upfront when disease is limited. Often time small bowel GIST is easily amenable to resection and can even be considered for laparoscopic resection [55]. Often times it is much easier to proceed to a segmental resection and primary anastomosis rather than perform a wedge resection (Fig. 59.21, panel a). GIST associated to neurofibromatosis type 1 is predominantly located to the small bowel and is virtually always multifocal (Fig. 59.21, panel b). Their risk does not depend in the number of lesions, while it depends on the features of the most aggressive one. Surgical resection may be directed only to remove the one or the ones at high risk, as removing

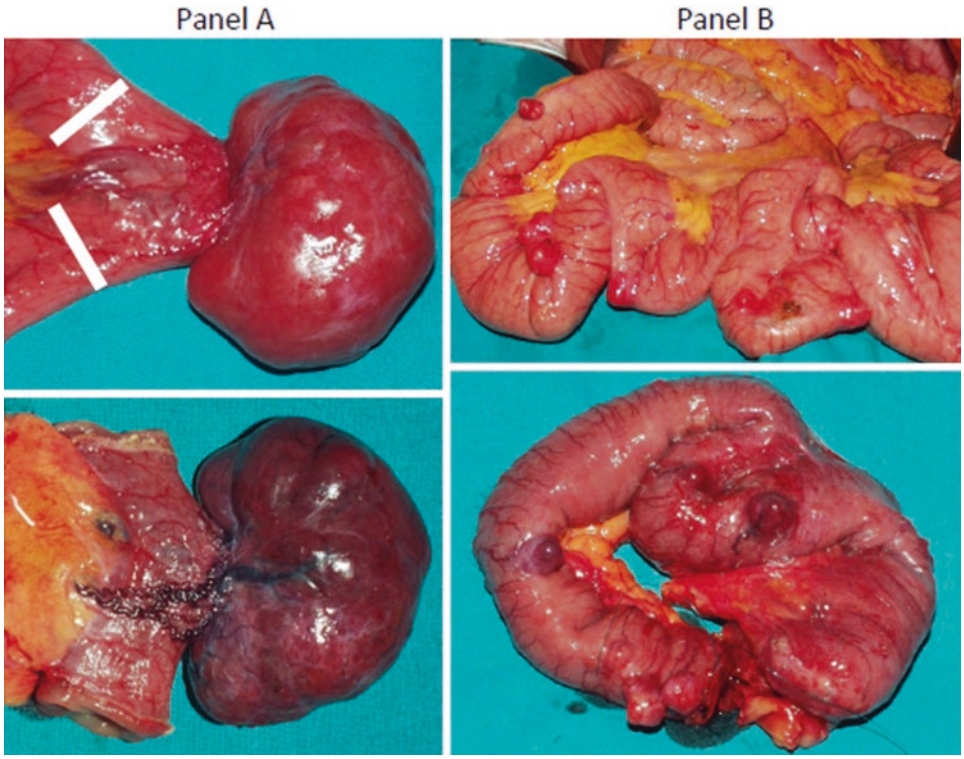


Fig. 59.21 Macroscopic appearance of a small bowel GIST and its implication for surgical management: single nodule, which can be resected with a simple small bowel segmental resection in panel **a**; multiple nodules (typical scenario in Neurofibromatosis type 1 patients), which can be resected with a more extended small bowel resection

all lesions may at times require an extended procedure followed by short bowel syndrome.

59.2.6 Rectal GIST

The most common site of presentation of colonic GIST is the lower rectum. Rectal GIST, while rare, often displays a more aggressive behavior than GISTs occurring in other locations [56]; indeed even small GISTs <2 cm with mitotic activity can recur and even metastasize [57]. Indeed, local recurrence rates are much higher than at other locations even after correcting for number of mitoses. Studies have shown that obtaining R0 margins of resection is paramount in rectal cancer for disease-free survival and overall survival. Neoadjuvant treatment with imatinib is associated with improved survival [58]. Depending on the size of the tumor, local approach to resection can be performed via transanal, transarcral, or perineal approaches (Fig. 59.22, panel a). It is important when performing a resection to achieve a complete removal of the tumor-bearing rectal wall and the tumor-covering tissue layer as GISTs originate from the muscularis propria and not the mucosa [58]. Often times if rectal GISTs are large and not amenable to local resection, abdominal resection or abdominoperineal resections should be undertaken (Fig. 59.22, panel b). There have been some case reports of laparoscopic techniques being used in rectal tumor resection, but the authors believe it should be undertaken only in small tumors when rupture-free and negative resection can be achieved.

59.2.7 Locally Advanced GIST

Perhaps, one of the important indications for neoadjuvant treatment is in the case of locally advanced borderline resectable GIST. Indeed, the conceptual advantage of therapy in these patients is twofold: first, the potential to avoid a multiorgan resection and organ preservation, thanks to tumor downstaging and the increased ability to obtain R0-negative resection margins (Fig. 59.23, panel a, b). Another advantage is the fact that treatment can render the tumor less vascular and friable allowing for easier manipulation and decreased risk of rupture which is key especially in larger or difficult to access tumors (Fig. 59.23, panel c, d) [59]. The use of imatinib prior to surgical intervention was based initially on institutional series demonstrating good radiologic responses of 60–70% with disease-free survival rates of 70% at 3 years [59]. In the radiation therapy oncology group, RTOG 0132 trial assesses the use of neoadjuvant imatinib in patients with locally advanced disease among others. Despite the short duration of neoadjuvant treatment in this cohort, the rate of R0 resection was 77%, quiet high in this fairly high-risk group [60]. A much larger 10 center retrospective study

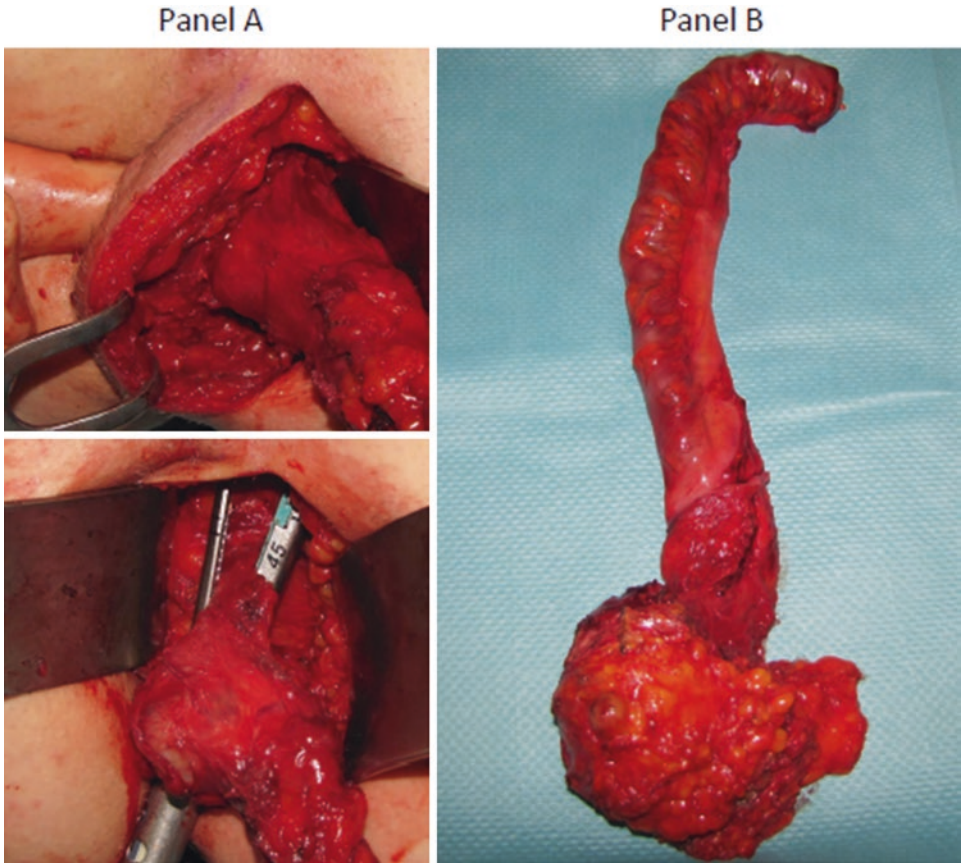


Fig. 59.22 Macroscopic appearance of a rectal GIST and its implication for surgical management: small nodule, which can be resected with a local approach in panel **a**; big tumor, occupying the whole pelvis, which can only be removed with an abdominoperineal resection in panel **b**

of neoadjuvant treatment with imatinib until maximal response was achieved or the lesion was no longer borderline. While the rate of R0 resection was of 80%, the rate of recurrence was 23% at 46 months [61].

There are particular clinical scenarios where neoadjuvant treatment is particularly important as tumor location might require an extensive, morbid resection with more complex long-term effects. In GISTs of the gastroesophageal junction, a two-cavity approach may be avoided by downstaging the tumor as it would be the case for duodenal GISTs where three patient might be spared a pancreaticoduodenectomy with all the possible morbidity it entails. Another important scenario is that of rectal GISTs where sphincter might be preserved and continence maintained, improving the patient's quality of life.

As impressive as the results obtained with neoadjuvant therapy, it is paramount for the surgeons to regularly assess the response to treatment. Indeed while the duration of preoperative treatment varies widely in the literature between 12 and 40 weeks and it does seem that optimal time for intervention is situated somewhere between 6 and 12 months. It is critical to assess response to treatment at the initiation of therapy and to continue this assessment regularly as not to miss the window of resectabilty. Moreover, the resection should occur ideally before the development of clonal resistance to the drug given.

59.2.8 Metastatic GIST

The main goal in the treatment of metastatic GIST at presentation is disease control, and the only way to do so is via systemic treatment as can be demonstrated by historical series where debulkings were attempted with dismal results with 25% median survival at 5 years [62]. While there remains a fervent debate on the utility of surgery in the setting of metastatic disease, there are some clinical scenarios in which patients might benefit from metastasectomy. The main rationale behind cytoreductive surgery in the era of third and even fourth line systemic therapy for GISTs is the concept of clonal resistance and the delay of subsequent lines of therapy [59]. It is important to recall that imatinib and other targeted therapies are not cytotoxic; rather, they produce cell senescence; they thus do not provide a cure for GIST.

Multiple institutional series have described promising results in disease control [63, 64]; however, patient

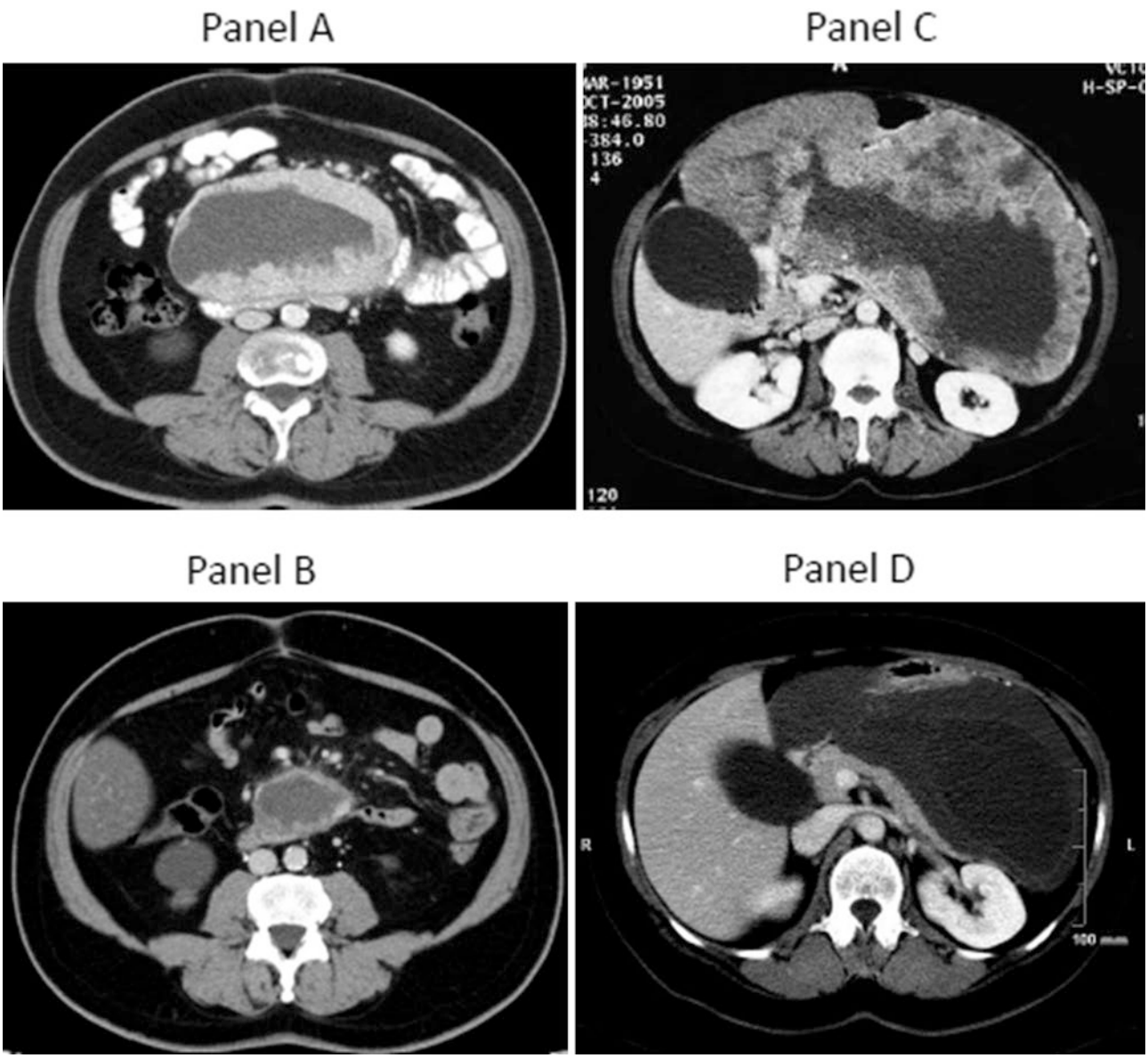


Fig. 59.23 Contrast enhanced CT scan, venous phase, of a primary large duodenal GIST abutting superior mesenteric vessels before (panel **a**) and after (panel **b**) 12 months of medical therapy with Imatinib: a major shrinkage has occurred, improving quality of surgical margins. Contrast enhanced CT scan, venous phase, of a primary large necrotic and highly vascularized gastric GIST before (panel **c**) and after (panel **d**) 12 months of medical therapy with Imatinib: no shrinkage has occurred, but an important change in tumor density has taken place with a significant reduction of vascularization, which makes tumor resection much less at risk of tumor rupture and safer

selection and optimal intervention timing are key when performing metastasectomies [65]. Indeed, patients with localized, persistent, and slow-growing metastases seem to benefit from surgical intervention much more than those with multifocal progression [59]. This might be secondary to the limited ability to obtain a complete debulkings in patients with multifocal disease. In a the large multicenter study by Bauer et al., an important prognosis factor in the patients selected for resection is site of disease with disease limited to the liver surviving significantly longer than those with peritoneal disease [63]. As with localized disease, the widow of opportunity after initiation of treatment with imatinib seems to be 6–12 months (Fig. 59.24, panel a, b) [63].

Some groups have suggested that cytoreductive surgery should be offered at the outset in order to clear all macroscopic disease. However, retrospective series did not find a survival advantage of initiating the treatment sequence with surgery. Moreover, surgery at the outset did not delay the initiation of second-line treatment [66]. Indeed starting the treatment sequence with imatinib allows for disease biology to declare itself and enables

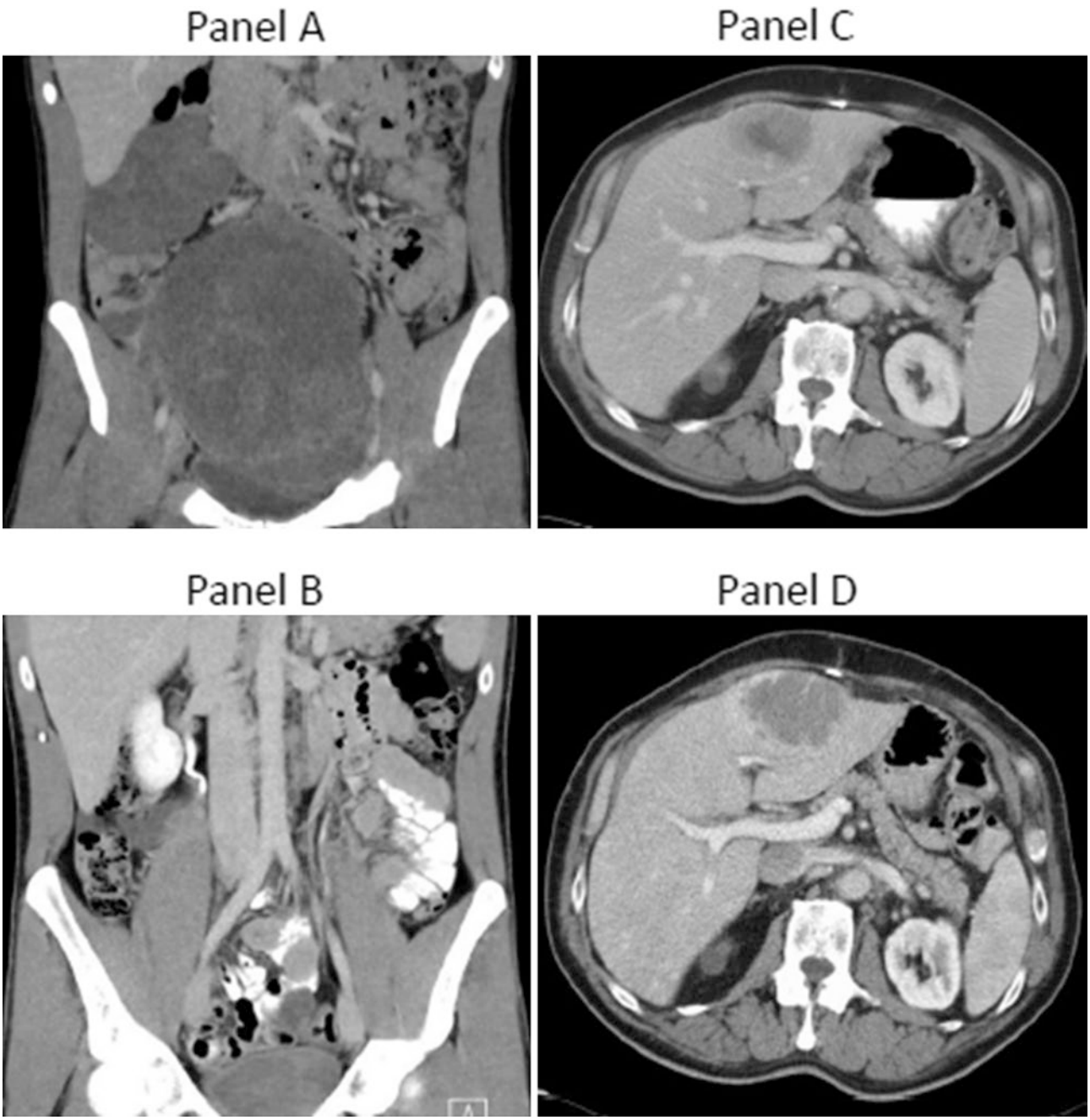


Fig. 59.24 Contrast enhanced CT scan, venous phase, of a large small bowel GIST metastatic to the peritoneum before (panel **a**) and after (panel **b**) 12 months of medical therapy with Imatinib: a major shrinkage has occurred of both primary and metastatic sites. Contrast enhanced CT scan, venous phase, of a single GIST liver metastasis before (panel **c**) and after (panel **d**) progressing on Imatinib: surgical resection of the single liver nodule is an option to consider

selecting patients that will have a favorable response to intervention. Another important factor in the choice of timing of intervention is disease progression. Indeed, patients undergoing interventions at the time of progression have shorter disease-free intervals postoperatively than those in remission at the time of intervention [64]. However, the use of surgery in limited progression may be of help to postpone the switch to a further line therapy, as this may maximize the time a patient stay on the given drug and therefore the control of the disease (Fig. 59.24, panel c, d) [63–65].

Another juncture when surgery could be considered for metastatic GIST is at the time of second-line therapy. In a study assessing survival in patients undergoing surgery for metastatic disease while on sunitinib, surgery was much less successful when compared to results

described in patients on first-line therapy, with lower macroscopically negative excision rates, higher complication rates, and lower survival [67].

Finally, surgery may play a role in the subgroup of TKI-insensitive GIST (PDGFRA D842V-mutated GIST or SDH-deficient GIST), as the natural history is usually more indolent and patients may survive several years with metastatic disease. The same does not apply to metastatic NF1-associated GIST, the prognosis of which is generally very poor.

59.2.9 Conclusion

Surgery remains the cornerstone treatment modality in GIST and the only one to provide a cure. Surgical techniques and their roles in the continuum of care are dictated by disease location and stage. With the advent of targeted therapies has been an increased utilization of neo-adjuvant imatinib in the treatment of localized disease leading to increased rates of complete resection and an associated disease free survival benefit. While surgery for metastatic GIST does remain controversial, there are certain patients that may benefit from resection especially when the disease is stable on systemic treatment and limited or an isolated progression has occurred.

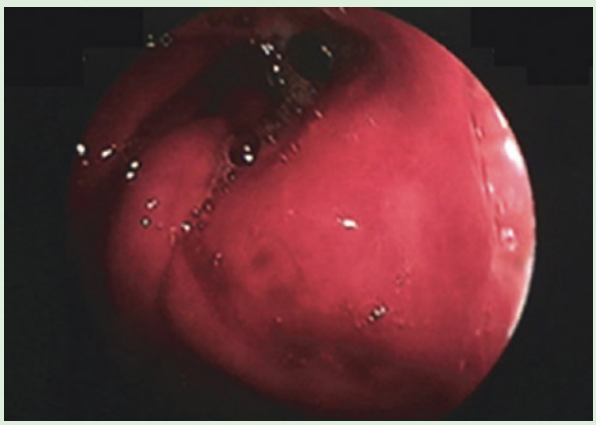
Summary of Clinical Recommendations

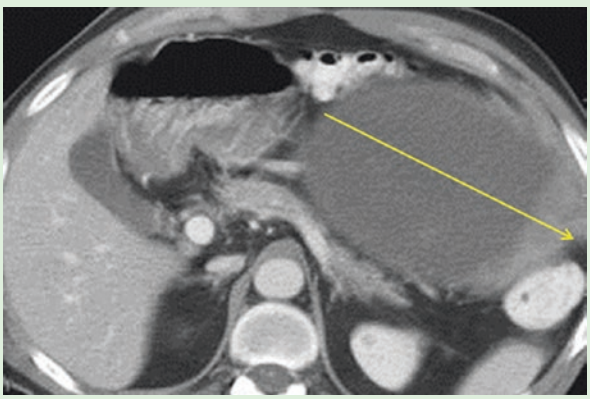
- *Linee Guida dell'Associazione Italiana di Oncologia Medica (AIOM)*
- *Sarcomi dei Tessuti molli e GIST. Edizione 2019.*
- *ESMO Clinical Practice Guidelines. Sarcoma and GIST.*
- *Annals of Oncology 2018*
- *NCCN (National Comprehensive Cancer Network) GUIDELINES FOR TREATMENT OF CANCER BY SITE-2018: Soft Tissue Sarcoma and GIST.*

Case Study Author: Please Indicate the Clinical Case TITLE Here

Man, 56 years old

- *Family history* negative for malignancy
- *APR:* Diabetes Mellitus type II
- *APP:* For nearly 2 months nausea and asthenia; diffuse abdominal pain
- *Objective examination*: Globose abdomen; mild tenderness on deep palpation (quadrant sup.sx); Palpable mass in the left hip
- *Blood tests*: Hb 9,1 g/dl; mildly impaired liver function tests (GOT; GPT)
- *Esofagogastroduodenoscopy*: Normal mucosa; compression of the gastric wall





- *TC abdomen mdc*: Lesion of 34 × 23 × 10 cm in continuity with small curvature, no cleavage plane from the gastric wall
- No lymphadenopathies
- Peritoneal implants and multiple liver metastases

Question

What action should be taken?

(1) Surgery (2) Biopsy (3) Other

Answer

Ecoendoscopy with biopsy

Histological examination:
GIST spindle cell; gastric origin
CD 117+; 2 mitosis/50 hpf

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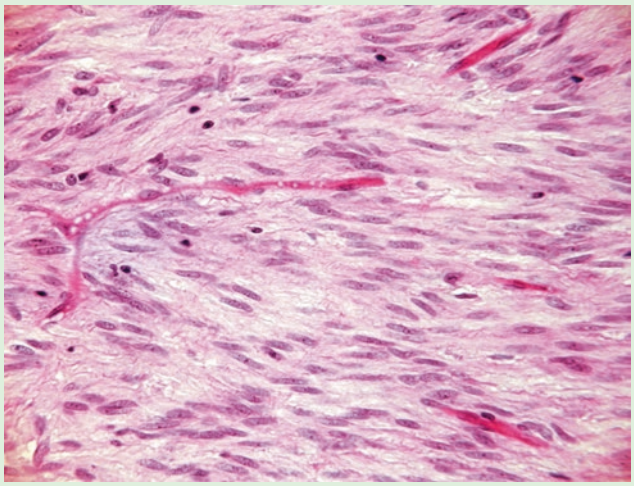
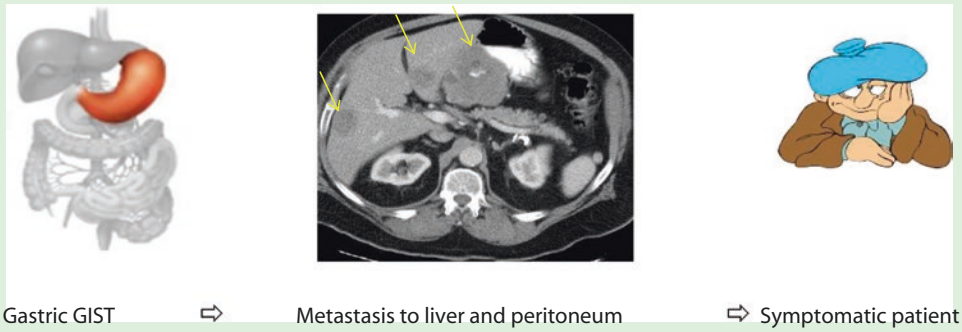




Gastric GIST ⇨ Metastasis to liver and peritoneum ⇨ Symptomatic patient

Question

What action should be taken?

(1) Surgery (2) Medical therapy (3) Mutational analysis

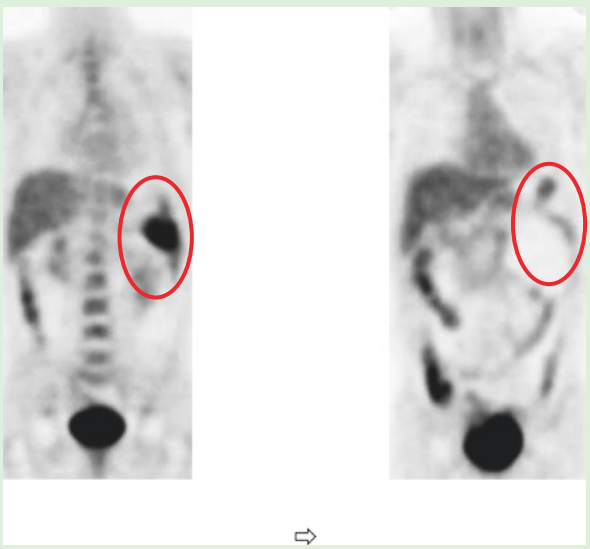
Answer

Mutational analysis: Exon 9 KIT mutation

⇩

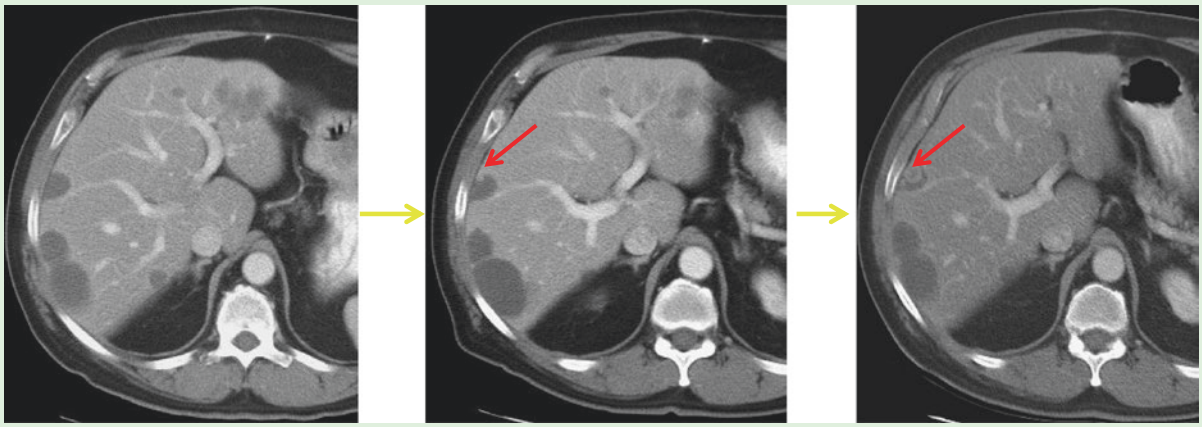
Medical therapy: Imatinib 800 mg/die

Response evaluation after 3 months of therapy with Imatinib 800 mg/die: Complete metabolic response to PET-FDG



Before Imatinib ⇨ After 3 months of Imatinib

Response evaluation after 12 months of therapy with Imatinib 800 mg/die: Appears "nodule in nodule" that increases in size after a further 2 months (14 months of therapy with Imatinib 800 mg/die)



After 9 months | After 12 months | After 14 months

Question

What action should be taken?

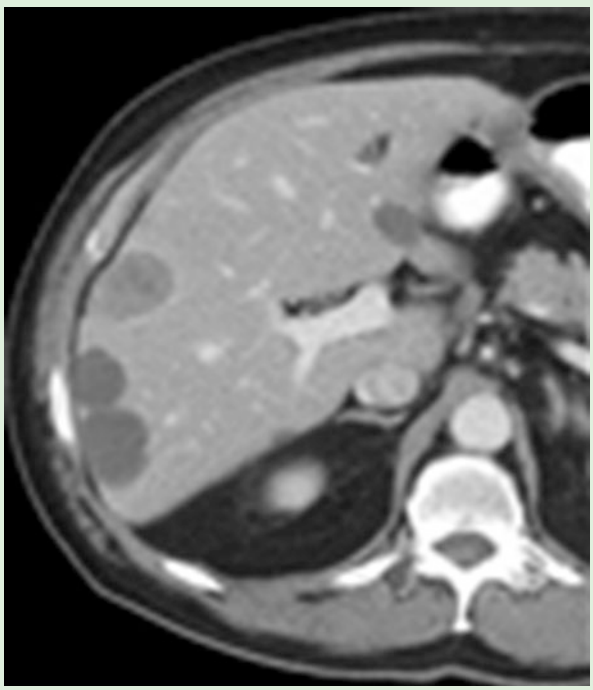
(1) Sunitinib (2) Regorafenib (3) Continues Imatinib 800

Answer

Begins Sunitinib 37.5 mg/die

Response evaluation after 3 months of therapy with Sunitinib 37.5 mg/die:

Tissue response to TC



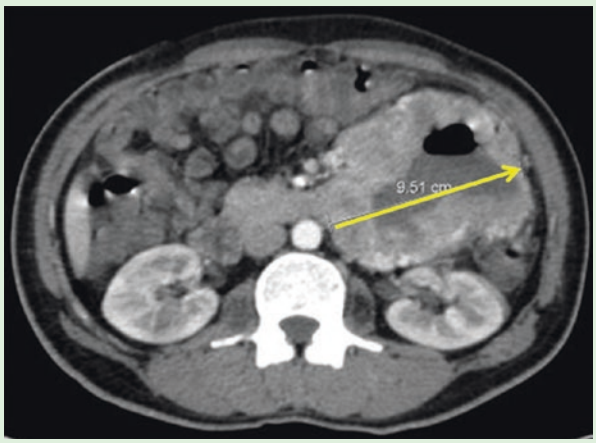
Key Points

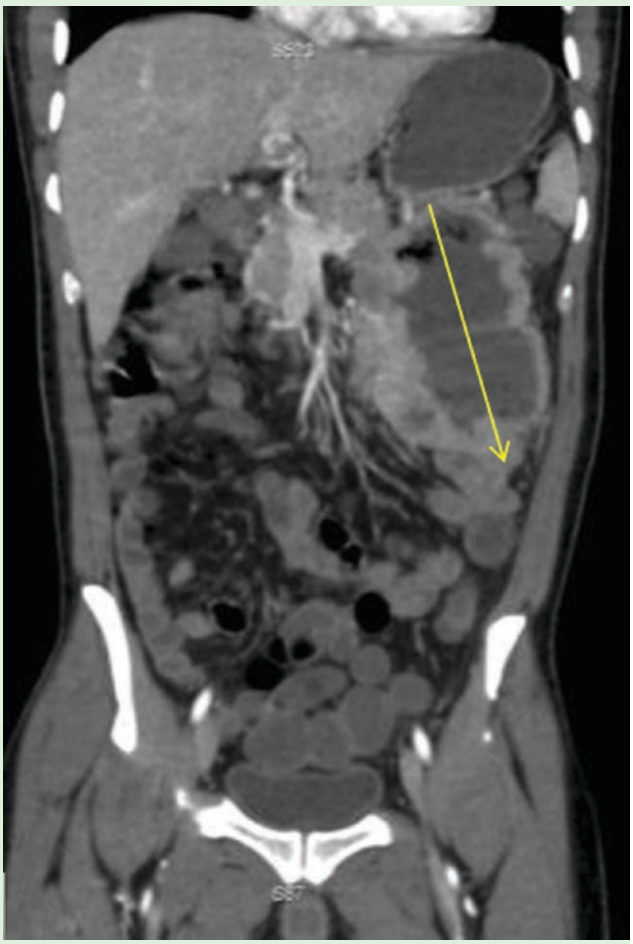
- The importance of a correct diagnosis: attention to the large bowel masses
- Symptoms often nonspecific; mucosa normally not involved
- The importance of a correct evaluation of the response
- Importance of mutational analysis in the therapeutic choice

Case Study Author: Please Indicate the Clinical Case TITLE Here

Man, 56 years old

- *Family history* negative for malignancy
- *APR*: negative
- *APP*: asthenia, dyspepsia, change in bowel habit
- *Blood tests*: Hb 9,2 g/dl
- *TC Abdomen mdc*: Voluminous abdominal lesion of 10 × 9.5 × 8 cm. located between stomach, spleen, pancreas, transverse colon and the first ileal loops. (localized disease)





Question

What action should be taken?

(1) Surgery (2) Biopsy (3) Other

Answer

Biopsy: GIST spindle cell, CD 117 + Mutational analysis: Exon 11 Kit mutation

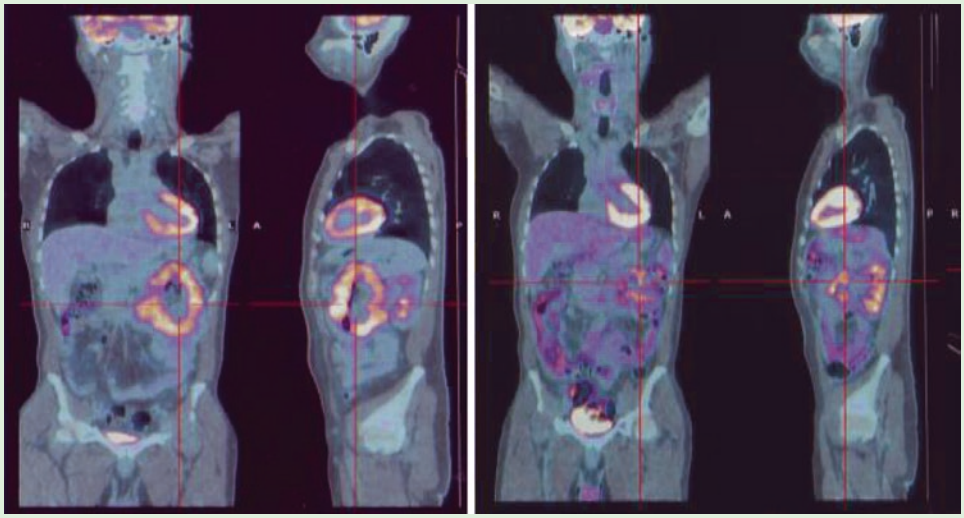
Question

What action should be taken?

(1) Surgery (2) Medical therapy (3) Other

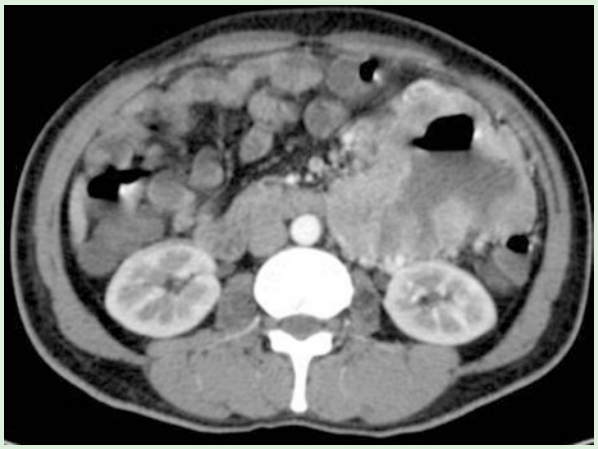
Answer

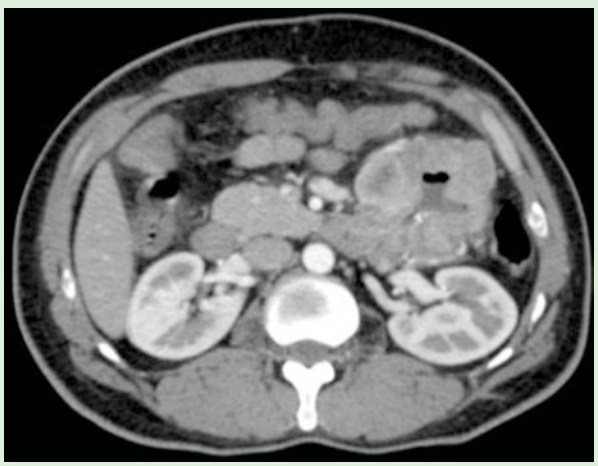
Preoperative treatment: Imatinib 400 mg/die



Before treatment

After 1 month of Imatinib





After 6 months of Imatinib: SD

Question

What action should be taken?

(1) Surgery (2) Continues Imatinib (3) Other

Answer

Surgery: R0

Key Points

- Importance of preoperative biopsy:
- Differential diagnosis with other neoplasia: Other sarcomas, germ cell tumors and lymphomas not need the same surgery!
- Possibility of medical treatment preoperative: it would be desirable to know the mutated exon before deciding whether or not to initiate a preoperative treatment
- Is appropriate to assess early response by PET
- The maximum response is obtained after 6–12 month

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Expert Opinion

Giuseppe Badalamenti

Key Points

GISTs are rare cancer that originate from the gastrointestinal tract; the most frequent location is stomach (55%), followed by small intestine (30%). Less frequent are colon/rectum (5%) and esophagus (<1%).

- Approximately 70% of GISTs are driven by mutations in the oncogene KIT; of those GISTs without KIT mutations, the majority harbor mutations in the gene encoding (PDGFRA) (15%). The remaining 15% of GISTs were described as KIT/PDGFRA "wild-type" GISTs.
- The mutational analysis is essential to predict the response to treatment with imatinib
- Surgery is the standard treatment in operable localized disease; locally advanced borderline resectable GIST or avoid multi-organ resection are the important indications for neoadjuvant treatment with imatinib. Surgery should be proposed between 6 and 12 months after starting a neoadjuvant treatment.
- In the case of high-risk GIST, an adjuvant treatment with imatinib for 3 years is the standard; in this case, the mutational analysis is mandatory to identify GISTs sensitive to imatinib.
- In metastatic setting, imatinib 400 mg is the standard treatment; in the case of GIST, exon 9 mutated, the treatment with imatinib high doses might be preferred. In the case of mutations resistant to imatinib, a clinical trial should be proposed.
- For GIST resistant to imatinib, sunitinib is indicated in the second line and regorafenib in the third line.
- Given the rarity of the pathology and the opportunity to participate in clinical trials, the patient's reference to highly experienced centers is always recommended.

Hints for Deeper Insight and Suggested Reading

- Recommendations for the implementation of mutational analysis and management of gastrointestinal stromal tumor (GIST) patients. Raccomandazioni 2019 per l'implementazione dell'analisi mutazionale e la gestione del paziente con Tumore Stromale Gastrointestinale (GIST). October 2019.
- Position paper of Italian Scientific Societies (AIOM – Fondazione AIOM – ISG – SIAPEC-IAP – SIBIOC – SICO – SIF). ► www.aiom.it
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