Gastrointestinal Stromal Tumors: An Update for the General Surgeon

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22.1 Introduction

Gastrointestinal stromal tumors (GIST) affect only 1% of patients diagnosed with neoplasms of the gastrointestinal (GI) tract. Despite their relative rarity compared to epithelial tumours, these are the most frequent neoplasms of mesenchymal origin in the GI tract. GISTs in fact are the most commonly diagnosed subtype of sarcomas overall. Other soft tissue tumours of the GI tract include lipomas, liposarcomas, leiomyomas, desmoid tumours, schwannomas and peripheral nerve sheet tumours.

GIST was recognized as a specific entity in the late 1980s based on clinical, histopathological and immunohistochemical features and was thought to be derived from smooth muscle cells given the spindle cell appearance at light microscopy. Today, a more likely derivation is the interstitial cells of Cajal (ICC).

22.2 Epidemiology and Clinical Features of GIST

The incidence of GIST is estimated at 7–15 new cases per million population per year. Autopsy studies do suggest though the incidence of subcentimetre gastric GIST (micro-GIST) might be as high as 30%. These lesions typically do not show any mitotic activity. The mean age at diagnosis lies at approximately 60 years with a slight predominance for the male gender.

GIST may arise anywhere in the gastrointestinal tract from the esophagus to the rectum. The stomach (40–60%) followed by the jejunum and ileum (25–30%) are the most common sites of origin. GIST of the duodenum (5%), esophagus (<1%), colon and

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M. W. Wichmann et al. (eds.), *Gastroenterology For General Surgeons*,
https://doi.org/10.1007/978-3-319-92768-8_22

rectum (5–15%) are rare. Due to accidental dispersion during embryogenesis, GIST can originate outside the gastrointestinal (<5%) tract, in the abdominal cavity, greater omentum and retroperitoneum. Tumors reach a median size of 5–7 cm at the time of diagnosis. Asymptomatic patients with much larger lesions are not uncommon.

An increasing number of GIST are asymptomatic and diagnosed accidentally by endoscopy or cross-sectional imaging (Fig. 22.1). Patients often present with nonspecific symptoms such as bloating, early satiety, unspecific abdominal pain or pain related to other pathologies. Fifty percent of patients with gastric GIST present with overt or occult bleeding due to erosion of the gastric mucosa over the subepithelial tumour (Fig. 22.2). Tumor rupture into the peritoneal cavity causing significant hemorrhage is rare.

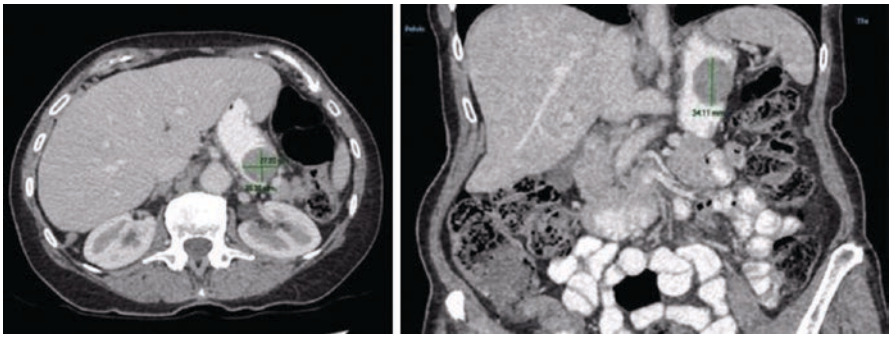

Fig. 22.1 Typical appearance of gastric GIST with endophytic growth pattern

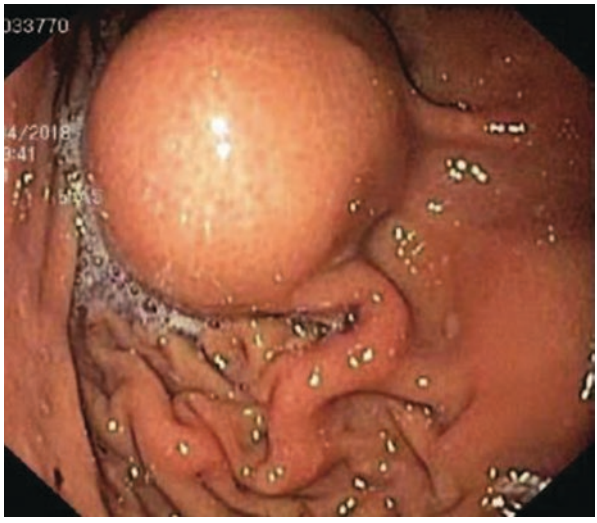

Fig. 22.2 Endoscopic view on a gastric GIST. Typical submucosal tumor with smooth surface without ulceration

Common sites of metastasis are the liver and the peritoneal cavity. Metastatic disease to the lung is uncommon in contrast to most soft tissue sarcomas. Lymph node metastasis is rare. Hypothyroidism and non-islet cell tumor hypoglycemia in a paraneoplastic setting have been described in isolated cases.

22.3 Molecular Features and Targets

The KIT proto-oncogene and its protein product, the KIT tyrosine kinase receptor (c-KIT, CD 117), are central for diagnosis and management of GIST. c-KIT is a transmembrane receptor with an extracellular binding site for stem cell factor (SCF). Binding of SCF to c-KIT leads to activation of multiple intracellular signalling cascades controlling cell proliferation, adhesion, apoptosis, survival and differentiation. "Gain of function" mutations in KIT lead to overexpression of the receptor tyrosine kinase KIT and subsequent tumorgenesis. The detection of overexpressed c-KIT receptors on the cell surface by immunohistochemistry and KIT mutations by DNA sequencing has contributed to discriminating GIST from other soft tissue neoplasms. Anoctamin 1 (DOG1) is a transmembrane chloride ion channel protein constitutively expressed in ICC and in the majority of GIST, including many KIT-negative GIST. CD34, a hematopoietic progenitor cell antigen, can be present on GIST but is less specific than KIT and DOG1. Commercial antibodies are available for epitopes on both proteins and present a helpful adjunct for diagnosing GIST.

Nearly 80% of GIST carry mutations in the KIT gene. Mutations in the KIT gene are usually limited to 1 of 4 of the 21 exons. Mutations in exon 11 are described in two thirds of GIST followed by exon 9 (7%), exon 13 (1%) and exon 17 (1%). About 10% of newly diagnosed GIST do not carry any mutations in the KIT gene but have mutations in the platelet-derived growth factor receptor alpha (PDGFRA) gene. PDGFRA is a receptor tyrosine kinase similar to c-KIT. Activating mutations in exon 12, 14 and 18 leads to histologically indistinguishable tumours compared to KIT mutation carriers. The remaining group of "wild-type" GIST has no detectable KIT or PDGFRA mutations. This group continues to shrink as gene mutations in BRAF, SDHF and neuro-fibromatosis 1 (NF1) have been discovered. Figure 22.3 shows structures, mutation sites and frequency of c-KIT and PDGFRA.

The type of mutation and the mutated gene has clinical relevance for diagnostic and more importantly treatment purposes. Anatomical tumor location, affected patient group and drug sensitivity are influenced by these factors as outlined in Table 22.1. The discovery of mutations in the KIT oncogene led to the ability to target the overexpressed c-KIT receptors. In 2001, Joensuu reported the first successful treatment of GIST using tyrosine kinase inhibitor (TKI) STI571 (imatinib mesylate, Gleevec™). This favourable result was confirmed in a larger cohort of patients, and GIST became the first solid tumour to be treated using a small molecule tyrosine kinase inhibitor.

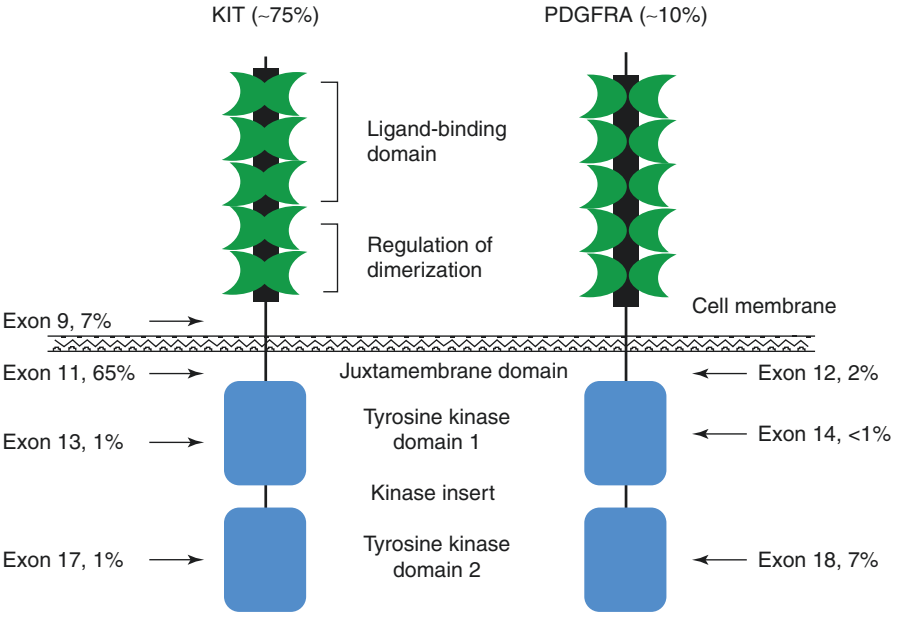

Fig. 22.3 Schematic structure of KIT and PDGFRA. The percentage indicate the frequency of mutations detected in each exon of the gene

Table 22.1 Classification of GISTs. Only the most common gene mutations are shown

Type of GIST	Incidence	Mutated gene	Clinical features	Imatinib sensitivity
Sporadic GIST				
KIT mutation				
Exon 9	~7%	*KIT*	Most non-gastric	Yes
Exon 11	~65%	*KIT*	Gastric or non-gastric	Yes
Exon 13	~1%	*KIT*		Variable
Exon 17	~0.5%	*KIT*		Variable
PDGFRA mutation				
Exon 12	~1.5%	*PDGFRA*	Most gastric	Yes
Exon 14	~0.1%	*PDGFRA*		Yes
Exon 18	~7%	*PDGFRA*	Most gastric	D842V insensitive. Most other sensitive
Wild-type (wt)	~10%	*KIT* wt, *PDGFRA* wt, sometimes *BRAF*, *SDHA*, *SDHB* or *SDHC* mutation	Gastric or non-gastric	Variable

22.4 Prognostic Determinants and Risk Stratification

GISTs often do not show classical histopathological features such as invasion and anaplasia/pleomorphism of cells and nuclei characteristic of many other cancers. Nearly all GISTs have the potential for malignant behaviour, and therefore a division into benign and malignant tumours is not useful in determining clinical management. As surgical resection remains the main pillar of GIST treatment, most risk stratification models are based on factors determined after resection of the tumors. These models predict progression-free survival based on factors described below. Güller et al. additionally found that nodal involvement, distant metastasis, older age, male gender and single marital status were associated with significant worse overall survival in a large population-based study including more than 5000 patients (see recommended reading).

Primary tumor site, tumor size and mitotic index independently predict risk of tumor recurrence after resection. In essence, tumors greater than 5 cm in diameter, with more than 5 mitotic figures per 50 high-powered fields and located outside the stomach (non-gastric GISTs), are associated with worse outcomes (Table 22.2).

Imaging is not routinely used to stratify recurrence risk. Several authors have reported computed tomography (CT) or endoscopic ultrasound (EUS) findings such as heterogenous enhancement, lobulated and/or exophytic growth pattern, mesenteric fat infiltration, ulceration and regional lymphadenopathy to be associated with higher risk of metastatic spread. Tumor rupture either spontaneous or intraoperative is an independent risk factor with a negative impact on disease-free survival.

The exact impact of the tumor genotype and kinase mutation status is confounded by the variable sensitivity of each gene mutation to imatinib. GIST with mutations in exons 9 and 11 seem to show a more aggressive phenotype compared to other mutation locations on the KIT gene. KIT exon 9 mutations are often found in non-gastric GIST. PDGFR gene mutations are nearly always found in gastric GIST and have a better outcome.

Table 22.2 Rates of progression-free survival for GISTs of the stomach and small intestine depending on tumour size and mitotic index

		Patients (%) with long-term progression-free survival	
Tumour size (cm)	Mitotic index (HPFs)	Gastric $n = 1055$	Small intestine $n = 629$
≤2	≤5/50	100	100
	>5/50	100	50
2–5	≤5/50	98.1	95.7
	>5/50	84	27
5–10	≤5/50	96.4	76
	>5/50	45	15
>10	≤5/50	88	48
	>5/50	14	10

22.5 Diagnostic Work-Up

Most GIST are now diagnosed by CT scan. Contrast (intravenous and oral)-enhanced CT of the abdomen and pelvis is the main imaging modality for staging. A typical GIST appears as a homogenous enhancing mass within the stomach wall or lumen (Fig. 22.1). Larger tumors might show intrinsic necrosis which appears as heterogenous enhancing mass. Large fungating and hyper-vascular lesions of the stomach might mimic primary liver lesions. MR imaging is reserved for specific anatomic locations such as rectum or duodenum. Assessment of extent of GIST metastasis in the liver is an indication for MRI.

Some gastric GIST might initially be found at endoscopy. The presence of a smooth submucosal mass in the stomach with or without overlying ulcer is pathognomonic (Fig. 22.2). The submucosal location direct biopsies are often not sufficient. Endoscopic ultrasound (EUS) allows for guided deeper fine needle aspiration (FNA) or core biopsies. GIST appear typically as hypoechoic, homogenous lesions with well-defined margins with EUS. Most GISTs originate from the muscularis propria (layer 4), but smaller lesions may arise from the muscularis mucosae (layer 2). EUS-guided core biopsies allow definite diagnosis of GIST by immunohistochemistry for KIT receptor presence and further allow assessment of KIT and other gene mutations. This is relevant for lesions where neoadjuvant treatment is considered due to anatomical location (esophagus, gastroesophageal junction, peripancreatic, rectum) in order to prevent potentially morbid or multivisceral resections. If the radiological appearance is typical and the perioperative risk is reasonable, histological confirmation by biopsy is not necessary prior to surgery.

Positron emission tomography using fluorodeoxyglucose (FDG-PET) is highly sensitive (86–100%) due to high glucose metabolism in GIST. However, specificity and anatomical definition are too low to consider FDG-PET as a primary diagnostic tool. Its main role is in accessing treatment response. Marked decreased glycolytic tumor metabolism can be detected as early as 24 h after treatment initiation with imatinib.

22.6 Principles of Surgery and Organ-Specific Aspects

Surgical resection of GIST remains the only established curative approach and is the treatment of choice. According to the long-term ACOSOG Z9001 trial, up to 70% patients with primary GIST of 3 cm and larger were cured by surgery alone. In general primary surgical resection is recommended for GIST larger than 2 cm in patients with life expectancy greater than 5 years and a reasonable perioperative risk profile. The natural history of GIST between 1 and 2 cm diameters is being researched regarding growth rate and metastatic potential. Kim et al. followed 948 patients with gastric subepithelial tumours smaller than 3 cm in a large retrospective study. Only 8.5% of these lesions $\leq$3 cm showed growth or changes in morphology over a median observation period of 24 months. Of the 25 patients who underwent surgical resection of the gastric subepithelial lesions, GIST was confirmed in 19. It is acceptable to

observe subepithelial lesions of 2 cm or less in diameter with no concerning morphological features using endoscopy or imaging. The optimal frequency of follow-up and specific risks of this approach, however, remains uncertain.

The goal of surgical treatment is resection of the tumour including its pseudocapsule. The aim is to achieve negative microscopic resection margins, but its positive impact on recurrence-free survival is not proven. It seems that other factors such as mitotic index and tumour size play a more significant role in determining the risk of recurrence irrespective of imatinib treatment. As previously mentioned, lymph node metastasis is rare (1%), and therefore regional lymph node resection is not warranted. GIST mostly show a displacing rather than invasive growth pattern independent from their size. At larger sizes, GIST induce significant growth of vasculature with large supplying arteries and veins. Even large GISTs may still have only a small attachment to the organ of origin and therefore can relatively be easily resected without affecting the adjacent organs. At larger sizes and following neoadjuvant treatment, GIST become increasingly friable and prone to rupture. Dissection should be performed with great care to prevent rupture associated with almost inevitable peritoneal tumor recurrence.

GIST of the esophagus are rare. Most submucosal lesions in the distal oesophagus are leiomyomas and not GIST. Well-circumscribed mesenchymal lesions that are >2 cm should undergo EUS and biopsy to confirm diagnosis due to the scope of operation needed to resect these tumors. Further consideration needs to be given to neoadjuvant imatinib to downstage these lesions. Due to the need of multimodal treatment, a referral and discussion within a multidisciplinary team are recommended. Local enucleation of GIST in the esophagus has been reported but has not been widely adopted due to lack of prospective outcome data using this approach.

Gastric GIST may arise from anywhere in the stomach but are most commonly found in the fundus. Laparoscopic resections have been widely adopted into surgical practice for resection of gastric GIST. Tumors up to a diameter of 6–8 cm are usually well suited for laparoscopic resection. Any surgical approach to the stomach starts with a careful assessment of the peritoneal surfaces and liver to assess for metastatic disease. A no-touch surgical technique and a plastic specimen retrieval bag are used to avoid peritoneal tumor seeding. An intraoperative resection margin of 1 cm is sufficient to achieve microscopic negative resection margins. Tumors arising from the anterior surface of the body/fundus and greater curvature are often amendable to resection with a wedge of stomach using an appropriate stapling device. Lesions originating from the posterior gastric surface or with an endoluminal growth pattern might need a trans-gastric approach via an open or laparoscopic gastrotomy. In both situations we find the simultaneous use of an endoscope to verify appropriate resection margins and as a guide for the stapling device to verify a patent stomach lumen very helpful. Resection of lesions in the antrum, at the incisura, lesser curvature, and gastroesophageal junction are more challenging due to the risk of luminal narrowing. In this setting additional strategies are may need to be considered including use of a bougie (50Fr), neoadjuvant imatinib for downstaging or a formal (partial) gastrectomy. These patients are often better managed by an experienced upper gastrointestinal surgical team with access to multimodal treatment options.

The small intestine is the second most common site of GIST. Jejunal and ileal GIST are removed with the tumor-containing segment of small bowel. Formal segmental lymph node resection is not indicated. Laparoscopic approaches with intracorporal stapled or extracorporeal small bowel anastomosis are the preferred approach. Management of duodenal GIST is more challenging from a surgical point of view. A multidisciplinary team approach and consideration of multimodal treatment in an experienced centre are warranted. Careful assessment of the tumor location in relation to the pancreas and the papilla of Vater is crucial. Preoperative downstaging with imatinib is often used to minimize the extent of resections. Small lesions away from the pancreas might be amendable to resection with a disc of duodenal wall. Depending on the extent of duodenal resection, direct tension-free closure might be achieved without compromising the lumen. Alternatively, a duodeno-jejunostomy in a Roux-en-Y configuration will need to be performed. Lesions in the third and fourth part of the duodenum are often amendable to segmental duodenal resection after a generous Kocher manoeuvre and division of the ligament of Treitz. Reconstruction can either be performed by direct end-to-end anastomosis to the proximal jejunum or as above, by a duodeno-jejunostomy with closure of the distal duodenum.

Rectal GIST benefit from additional imaging with a pelvic MRI to define local involvement due to the missing serosal layer of the rectum and proximity to the anal sphincter. Neoadjuvant imatinib can downstage the tumor and improve outcomes when compared to rectal surgery alone. Standard open and laparoscopic resection strategies as well as trans-anal resection approaches have been described.

22.7 Neoadjuvant and Adjuvant Imatinib Mesylate

GIST respond poorly to almost all standard chemotherapy agents and radiotherapy. Imatinib mesylate (STI571, Gleevec) is the first agent to exhibit a significant activity in GIST. Imatinib inhibits tyrosine kinases such as KIT and PDGFR and is now considered the standard first-line treatment for advanced GIST. At a usual dose of 400 mg orally once daily, the treatment is well tolerated with common adverse effects that include periorbital edema, muscle cramps, diarrhea and anemia. Approximately 15% of GIST are resistant to imatinib such as carriers of KIT exon 9 mutations. Response to imatinib can be estimated by mutation analysis or observed by imaging. GIST typically respond by transformation from dense lesion into cyst-like structures under imatinib treatment. This morphologic transformation is often the only sign of response exhibited by the tumour and is especially important in accessing the response of imatinib in the neoadjuvant setting.

There have been no trials comparing surgery first with neoadjuvant imatinib followed by surgery. It is a common practice nowadays to consider neoadjuvant treatment in the setting of locally advanced lesions to prevent extensive organ or

multivisceral resections as aforementioned. The goal is to downstage tumors to allow for safer and less morbid surgical interventions. Standard chemotherapy response criteria (RECIST) do not work well in GIST. Despite often immediate metabolic changes within the tumour seen in FDG-PET scans, decreased tumor size will only be seen after several weeks of treatment. In practice, a CT and FDG-PET 4 weeks after treatment initiation with imatinib might not show significant tumor shrinkage but often shows a decrease in tumor density, a morphologic cystic transformation and a decreased metabolic activity. Failing this, tyrosine kinase inhibitor resistance needs to be considered. Unlike other chemotherapy agents, imatinib can be continued up to the time of surgery and restarted straight after as there are no immunosuppressive effects and no negative impact on wound healing.

Adjuvant imatinib was established in the landmark ACOSOG Z9001 trial. In this study, over 700 patients with operable GIST (diameter > 3 cm) were randomized to either receive placebo or imatinib 400 mg daily for 1 year following surgical resection. The trial was stopped at interim analysis due to significantly improved progression-free survival in the imatinib group. One-year recurrence-free survival was 98% in the imatinib group and 83% in the placebo group. Adjuvant imatinib was well tolerated with a low rate of serious adverse events in the treatment group. As demonstrated in Fig. 22.4, the progression-free survival curves seem to converge after 3 years. This might indicate that imatinib is effective in controlling

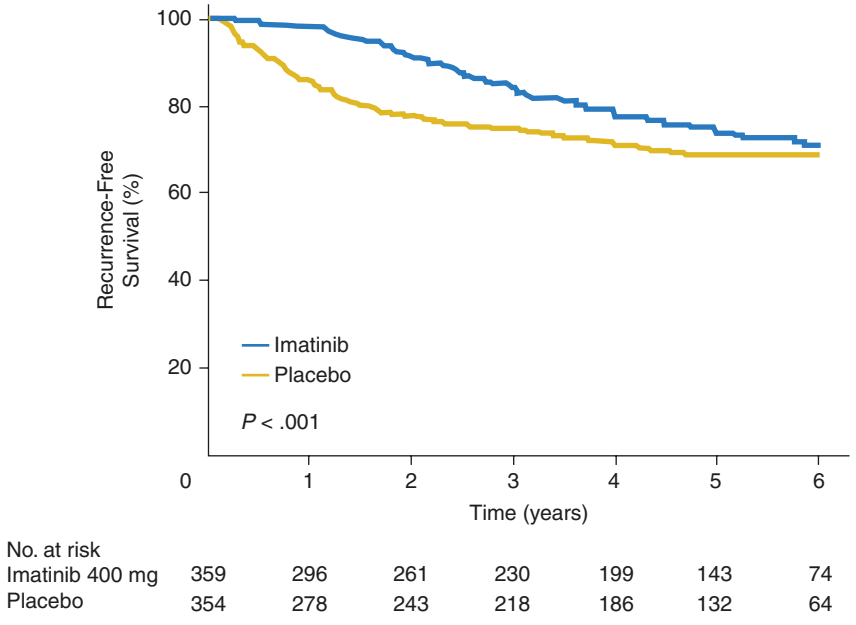

Fig. 22.4 Recurrence-free survival of patients with primary GIST of 3 cm or greater after complete resection, randomized to 1 year of adjuvant imatinib vs. placebo

residual disease but is not able to clear it. Further studies are underway to clarify the optimal duration of adjuvant treatment with imatinib. Current recommendations are for adjuvant therapy with imatinib for 3 years following primary resection of high-risk lesions.

22.8 Role of Surgery in Metastatic and Recurrent GIST

Although imatinib has become the first-line treatment for recurrent and metastatic disease, there remains a role for surgery. In the setting of recurrent diseases, median progression-free survival with imatinib is 24 months. Development of secondary mutations in tumour subclones is thought to be responsible for imatinib resistance. Second- (sunitinib) and third-line (regorafenib) tyrosine kinase inhibitors (TKI) are indicated but show less durable response rates. The goal of secondary metastasectomy or debulking surgery is to remove tumour mass before resistance to second- and third-line TKI develops and to stop disease progression by eliminating resistant clones. This approach has not been tested in prospective randomized trials due difficult accrual of patients. Several retrospective single-institution studies report long-term disease control and longer overall survival in selected patient groups (i.e. stable disease, focal progression only, partial responders and isolated sites of progression) with this approach.

The liver and the peritoneum are the most common sites of metastatic disease. It is estimated that around 25–30% of patients presenting with recurrent/metastatic disease are technically resectable. The ideal timing for surgery is unknown. The median time to best response is 3.5 months, and little further tumour downsizing is reported after 9 months. TKI treatment should continue after metastasectomy or debulking procedures. Liver metastasis is approached similar to colorectal liver metastasis. Treatment is focused on clearing the liver from any disease using resectional and/or ablative techniques. Limited data is available on long-term outcomes of hepatic artery embolization, chemoembolization or radioembolization using yttrium-90-tagged microspheres in patients with unresectable liver disease. Removal of peritoneal metastasis might necessitate en bloc resection with other intra-abdominal organs.

22.9 Summary

GIST is a rare neoplastic disease affecting the entire gastrointestinal tract only known as specific entity for the last 40 years. Discovery of molecular mechanisms involved in the pathogenesis of this tumour has led to the development of targeted therapies. Disease pathology ranges from clinically irrelevant micro-GIST to highly aggressive neoplasms presenting with widespread metastasis and therapy-resistant genetic mutations. Given the complex clinical behaviour and highly variable genetic background, a multidisciplinary team approach is warranted for these patients. Figure 22.5 summarizes the therapeutical approach to primary and recurrent/metastatic GIST.

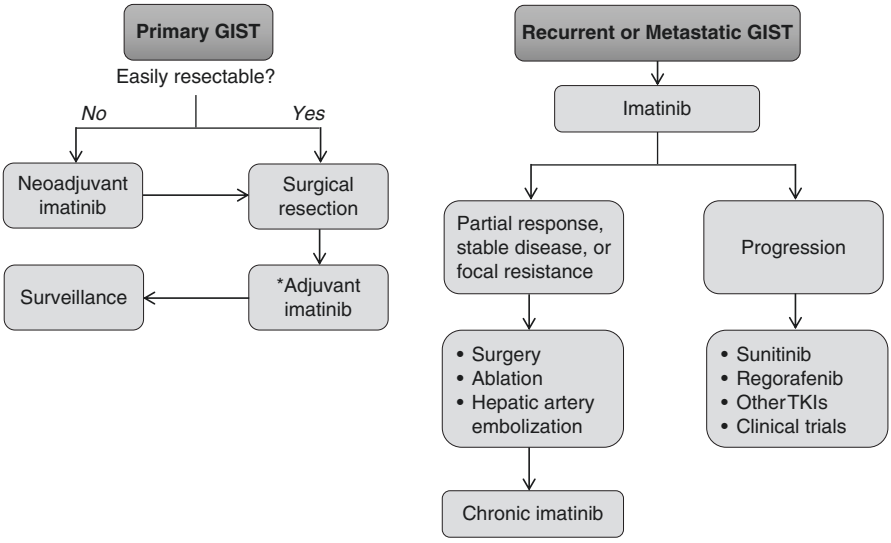

Fig. 22.5 Summarized approach to primary and metastatic/recurrent GIST

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