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ORIGINAL ARTICLE

Gastrointestinal Stromal Tumors (GIST): an Overview

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Abstract
Gastrointestinal stromal tumors are rare mesenchymal tumors of the alimentary tract with varied clinical presentation ranging from small asymptomatic tumors detected incidentally to large palpable abdominal masses which may present with gastrointestinal bleeding, perforation, or obstruction. CT abdomen is the imaging modality of choice. Treatment depends upon the size, location and risk stratification. Complete surgical excision is the treatment of choice for resectable tumours. The discovery of c-kit mutations and tyrosine-kinase inhibitors has revolutionized the treatment of locally advanced, metastatic and recurrent tumors.

Keywords gastrointestinal stromal tumors · imatinib · *c-kit* mutation

Introduction

Gastrointestinal stromal tumor (GIST) is a rare stromal neoplasm that accounts for 5% of all soft tissue sarcomas. It is the most common mesenchymal neoplasm of the gastrointestinal tract. GIST defines a distinct group of gastrointestinal tumors that originate from the interstitial cells of Cajal [1]. These cells act as regulators of bowel peristalsis and are also called *pacemaker cells*, providing an interface between autonomic nerve stimulation and the muscle layer of the gastrointestinal wall. GISTs are rare cancers, which were defined as a distinct disease in the 1990s, having been classified within smooth muscle neoplasms for decades from their first description in the 1960s.Coincidentally, in 2000, they became targetable by new tyrosine kinase inhibitors (TKIs), given the role played by KIT and platelet-derived growth factor receptor alpha (PDGFRA) in their pathogenesis.

Epidemiology

GIST represents the most frequent mesenchymal tumor in the gastrointestinal tract, accounting 0.1–3% of gastrointestinal malignancies [2]. The annual incidence is approximately 15 per million per year [3].Improved detection on histopathological specimens has contributed to a dramatic increase in its incidence, although the true incidence may also be increasing.

With a slight male predominance, GISTs are mostly found in adults > 40 years of age, with a median age of 60–65 years. Predominantly sporadic, but a small subset of GISTs (≤ 5%) occurs in familial multitumor syndrome. In decreasing order of frequency, the four most important GIST syndromes are type 1 neurofibromatosis (wild-type GISTs mainly in the small bowel and possibly multicentric), Carney's triad (gastric GIST, pulmonary chondroma, and extra-adrenal paraganglioma), familial GIST syndromes (germline mutations in c-Kit/PDGFRA), and Carney–Stratakis syndrome (GIST, familial paraganglioma) [3, 4].

GISTs are submucosal tumors that arise in the digestive tract. The stomach (60%) and small intestine (30%) are the most common primary sites; the duodenum (5%), colon and rectum (< 5%), esophagus and appendix (< 1%) are less common primary sites. Rarely, GISTs develop within the mesentery, omentum, or retroperitoneum (labeled as extra-gastrointestinal GIST) [3–5].

Histopathology

The differential diagnosis of a subepithelial tumor arising in the gastrointestinal tract is broad, and histologic findings observed on hematoxylin and eosin-stained sections are not specific for GIST. The cellular morphology of GISTs is mainly divided into three categories, namely, the spindle cell type (70%), epithelioid type (20%), and mixed type (10%) [5, 6]. While gastric, small intestinal, and colonic GISTs are mostly composed of spindle cell

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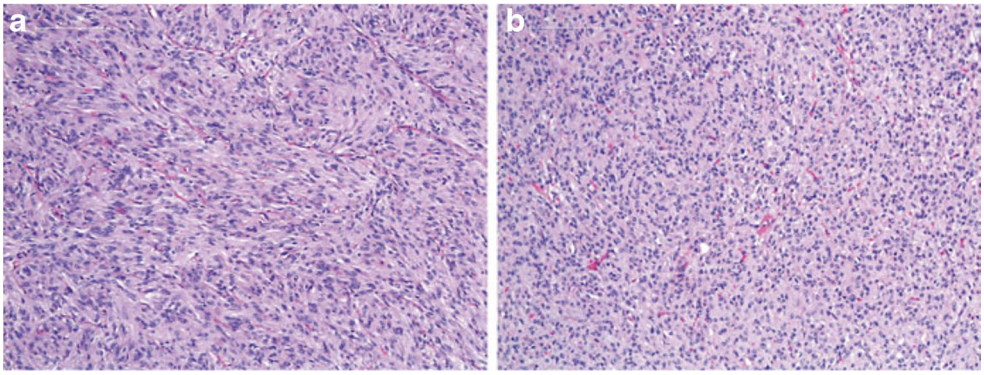

Fig. 1 Histologic subtypes of GIST (**a**) GIST, spindle cell type (**b**) GIST, epitheloid type. (Courtesy of Anja Schmitt, MD, Department of Pathology, University Hospital Bern)

tumors, KIT-negative GISTs commonly have epithelioid type cells [3]. Figure 1 shows the histologic subtypes of GIST. Importantly, there are no pathologic clues to make a distinction between malignant GISTs and others whose clinical behavior is actually benign. It follows that all GISTs are currently considered malignant neoplasms, although with a highly variable risk of distant relapse. This is the reason why risk classification systems are generally used in the clinic as prognosticators, being based today on a pathologic factor (i.e., the mitotic count) and two clinical variables (tumor size and tumor site).

Immunohistochemistry

Immunohistochemically, most GISTs (> 90%) show strong positivity for KIT (CD117) and negativity for desmin and S100 that are positive in smooth muscle and neural tumors. CD34 antigen (70%), smooth muscle actin (SMA, 30–40%), desmin (< 5%), and S100 protein (~ 5%) are among the other markers which are expressed [3, 7]. A small subset of GISTs lacks the characteristic KIT mutations, in a proportion of which activating mutations in the related RTK, PDGFRA were detected. But immunohistochemical status does not reflect the mutational status with regard to KIT and PDGFRA, per se, so that it has no concrete predictive value for sensitivity to TKIs. In absent c-KIT and PDGFRA mutation, SDH-B mutation is done to rule out wild-type GIST. DOG1 is calcium-dependent, receptor-activated chloride channel, expressed independent of mutation. In PDGFRA mutation, generally, KIT mutation is low, and DOG1 is high. Overall positivity is near 99% [3, 5]. GISTs must be differentiated from other soft tissue tumors of the gastrointestinal wall, including those of smooth muscle and neural origin and desmoid-type fibromatosis, endocrine tumors, melanocytic tumors, and lymphomas.

Molecular Pathology

Molecularly, GISTs have become a relatively heterogeneous and complex group of lesions. Gain-of-function mutations of the oncogenes located on chromosome 4 (4q12) coding for the type III receptor tyrosine kinases KIT and PDGFRA can be found in approximately 80% of GISTs. Pathogenetically, they are the drivers of the disease and, therapeutically, underlie the efficacy of currently used TKIs. They are mutually exclusive and result in the constitutive activation of either KIT or PDGFRA, which normally are autoinhibited, being activated by the binding of their respective ligands (i.e., stem-cell factor [steel factor] and platelet-derived growth factor A). Mutations can be deletions, insertions, and missense mutations. They affect exon 11 (70%), exon 9 (10%), exon 13 and 17 (1% each) of KIT. Approximately, 10% of GIST have mutations homologous to these, which affect PDGFRA (i.e., exon 12, 14, and 18 of the oncogene, with 70% being represented by exon 18 D842V mutation) [3, 8, 9]. Figure 2 shows the activation of KIT, and Fig. 3 depicts the various mutations associated with KIT or PDGFRA.

Some tumor cell mutations correlate with elective primary sites of origin. In particular, exon 9 mutations of KIT are preferably found in the small bowel, and PDGFRA mutations are found in the stomach.

Clinical Presentation

The clinical manifestation of GIST is widely variable, depending on tumor location and size. Tumor size is extremely variable, ranging from small lesions to large masses. Small tumors are usually asymptomatic and are diagnosed incidentally during imaging, endoscopy, or surgery. GISTs may remain indolent because of their submucosal origin and tendency to grow exophytically [10]. Most are exophytic subserosal lesions, while others are endophytic polypoidal submucosal masses that are prone to surface ulceration and bleeding. Tumors have soft or rubbery consistency, and larger tumors may undergo cystic degeneration, hemorrhage, or necrosis (Figs. 4 and 5).

Symptoms and signs are not disease-specific but are related more to the site of disease. Symptomatic GISTs are usually large and may present with gastrointestinal bleeding from mucosal ulceration (hematemesis, melena, or symptoms and signs of anemia). Other symptoms include vague abdominal complaints (early satiety, bloating, loss of appetite, nausea, vomiting), abdominal

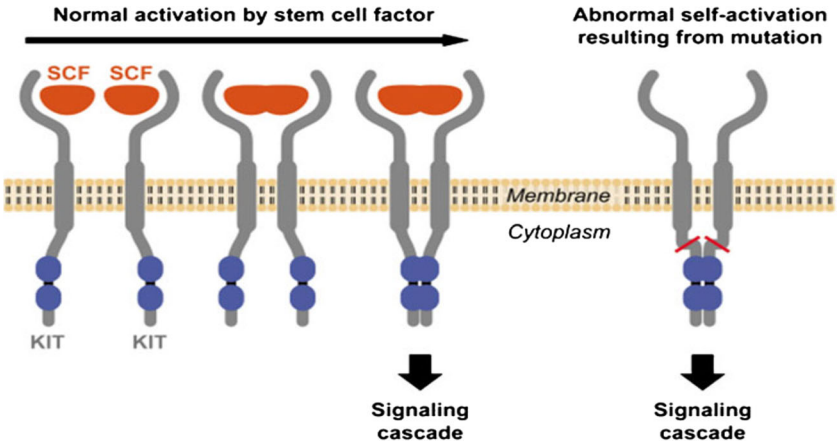

Fig. 2 Activation of KIT. Two KIT receptors normally dimerise in the presence of the ligand stem cell factor (SCF) to initiate downstream signaling (left). Mutations in the receptor cause abnormal constitutive signaling without stimulation from the SCF ligand (right) (Hornick JL, MDPhD, Harvard Medical School, Department of Pathology, Boston, MA, and Lazar AJF, MD PhD, Sarcoma Research Center, M. D. Anderson Cancer Center Houston, Texas, reproduced with permission from GIST Support International)

fullness, and pain. A palpable mass may also be present. The submucosal location of the tumor may cause obstruction or perforation. Esophageal tumors may present with dysphagia, and those arising in the duodenum may compress the adjacent pancreatic head, resulting in jaundice. Rectal GISTs may present with symptoms of mass effect such as frequency, hesitancy, or poor urinary stream due to invasion of the urinary bladder. Intra-abdominal or intraluminal hemorrhage can occur, and rupture into the peritoneal cavity is possible. This life-threatening complication also carries a high risk of dissemination by peritoneal seeding of the tumor [3, 7, 10].

A range of 15–50% of GISTs may have metastatic disease at presentation. Metastasis occurs usually to the liver and peritoneum. The pattern of spread is almost entirely intra-abdominal with < 5% cases having pulmonary metastases. It virtually never spreads to regional lymph nodes, however there may be invasion of adjacent organs as intestine, liver, or bladder. Diffuse peritoneal spread may manifest as innumerable small tumor nodules essentially replacing the omentum, studding the diaphragmatic surface and peritoneal lining, or covering the serosal surfaces of the bowel. In these cases, tumor-associated ascites is typical [7].

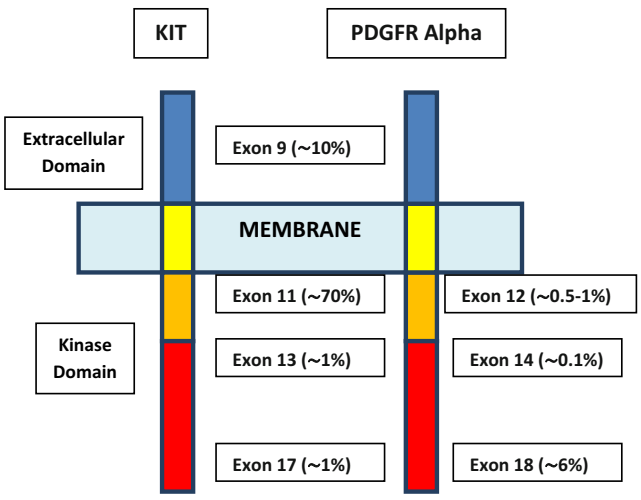

Fig. 3 Mutations associated with KIT and PDGFRA (Adapted from Corless et al. Annual Review of Pathology: Mechanisms of Disease 2010)

Diagnosis and Staging

Endoscopic ultrasonography (EUS) is a useful tool for diagnosing GIST (especially for small esophageal or duodenal nodules < 2 cm) [4]. Lesion can be visualized, and guided fine-needle aspiration biopsy (EUS-FNAB) can be taken. Cystic spaces, echogenic foci, irregular borders, and tumor size more than 4 cm on EUS have been identified as independent factors associated with malignancy [11]. However, tumor rupture or dissemination may occur following biopsy, hence pre-operative biopsy is not essential in a resectable tumor. Conversely, biopsy may be needed if atypical radiologic features are present, or pre-operative treatment has to be given for unresectable tumor. Percutaneous or laparoscopic biopsies should be avoided given the risk of tumor cell seeding [4, 7].

Contrast-enhanced CT of abdomen and pelvis is the imaging modality of choice to diagnose GIST and pick up peritoneal and liver metastasis [3]. While GIST typically appears as well-circumscribed, brightly enhancing masses arising from the GI tract as extraluminal, occasionally exophytic masses [10]; characteristics such as size greater than 10 cm, calcifications, irregular margins, heterogeneous, lobulated, regional lymphadenopathy, ulceration, extraluminal, and mesenteric fat infiltration are more likely to be associated with metastasis [12]. MRI provides better preoperative information for rectal GISTs and in detecting liver metastasis, hemorrhage, and necrosis. CT or radiography of the chest and routine laboratory

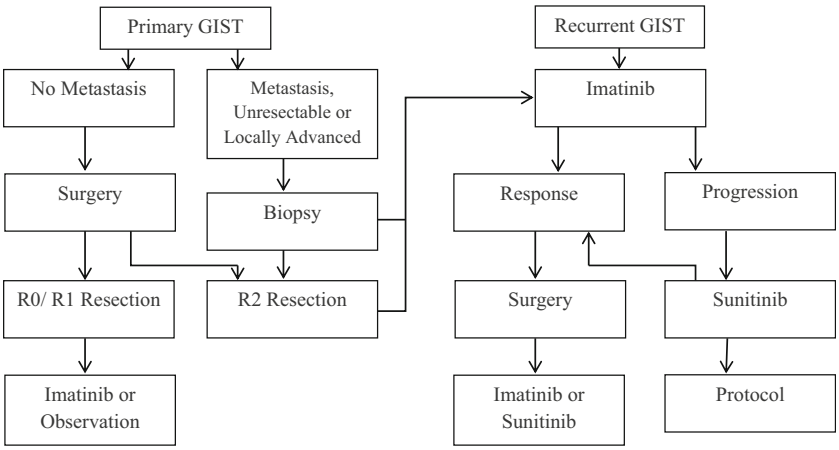

Fig. 4 Algorithm showing Management of Gastrointestinal Stromal Tumours [R0 (grossly and histologically negative margin), R1 (grossly negative but histologically positive margins), R2 resection (grossly positive margins) [Adapted from Raut CP et al Gastrointestinal Stromal Tumors of Gastric Origin from The Biology of Gastric Cancers Springer 2009]

tests complete the staging work-up. Role of PET scan is in finding early response of TKIs in neoadjuvant setting, differentiation of necrotic from inactive scar area, and in deciding malignant from benign disease [3, 7, 13]. Preoperatively, given TKIs response can be seen in 2–4 weeks via PET scan and in 4–8 weeks in CT/MRI [13].

Mutational analyses for known mutations involving KIT and PDGFRA genes should be considered prior to exploration to confirm the diagnosis if there is doubt, and it also predicts response to therapy with TKIs.

Risk Stratification

Current risk classification systems are based on the combination of mitotic count, tumor size, and site of origin. Indeed, the mitotic count (expressed as the number of mitoses per 50 high-power fields on a total area of 10 mm^2) is the main prognostic factor, proportionally correlating to the risk of relapse. Tumor size is the next prognostic factor. With regard to the primary site, gastric lesions have a better prognosis than small bowel and rectal GISTs. Table 1 illustrates the risk associated with GIST situated in various parts of gastrointestinal tract [3].

Spontaneous or post intervention rupture of tumor is an independent risk factor that indicates poor prognosis [3, 4]. At present, mutational status has not been included in the risk stratification.

The maximum risk interval averages 2 to 3 years after surgery, or if an adjuvant therapy was done after its completion. Long-term relapses are unlikely, although they are occasionally observed, especially in GISTs with low mitotic rates.

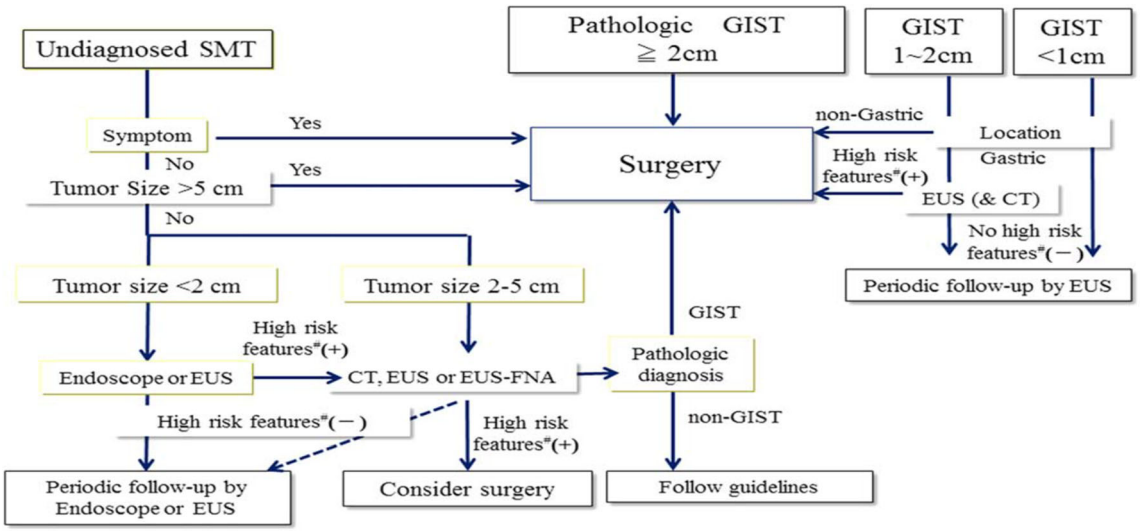

Fig. 5 Algorithm to Approach of pathologically undiagnosed Submucosal tumors (SMTs) and pathologically confirmed Gastrointestinal stromal tumors (GISTs) are illustrated. Therapeutic approaches for pathologic GISTs are divided by size (i.e, 2 cm, 1-2 cm, and < 1 cm). High-risk features include irregular border, cystic spaces, ulceration, echogenic foci, heterogeneity, and progression during follow-up. CT indicates computed tomography; EUS, endoscopic ultrasonography; EUS-FNA: endoscopic ultrasonography guided fine-needle aspiration biopsy. (Adapted from Nishida T et al Diagnostic and Treatment Strategy for Small Gastrointestinal Stromal Tumors from Cancer 2016)

Table 1 Armed Forces Institute of Pathology (AFIP) classification

Tumor parameter	Risk for progressive disease (defined as metastasis or tumor-related death)				
Mitotic index (counts per 50 HPF)	Size (cm)	Gastric (%)	Duodenum (%)	Jejunum or ileum (%)	Rectum (%)
< 5	≤ 2	None (0)	None (0)	None (0)	None (0)
	> 2 ≤ 5	Very low (1.9)	Low (4.3)	Low (8.3)	Low (8.5)
	> 5 ≤ 10	Low (3.6)	Moderate (24)	n.a.	n.a.
	> 10	Moderate (10)	High (52)	High (34)	High (57)
≥ 5	≤ 2	None (0)	n.a.	n.a.	High (54)
	> 2 ≤ 5	Moderate (16)	High (73)	High (50)	High (52)
	> 5 ≤ 10	High (55)	High (85)	n.a.	n.a.
	> 10	High (86)	High (90)	High (86)	High (71)

Adapted from Miettinen and Lasota (2006)

Management

The management of GIST depends on many factors, and the decision regarding this should involve a multidisciplinary team consisting of pathologist, diagnostic radiologist, surgeons, and oncologists.

The goal of treatment is to provide symptomatic relief and if possible complete excision of the tumor. Patients with resectable tumor have three times better survival than those with unresectable disease [14]. While GIST > 2 cm are considered to be potentially malignant, gastric GIST ≤ 2 cm usually have a benign course. Most of the guidelines propose an initial follow-up of tumor by EUS at 6 months interval and subsequent annual follow-up until there is progression in tumor size, symptoms, or high-risk features on EUS. Surgery is indicated for tumors > 2 cm, proven malignant tumors, and tumors with high-risk features on EUS or those that increase in size during follow-up. Surgery is also recommended for GIST located in the small intestine, colon, or rectum given their potential for being malignant [6]. The advent and use of TKIs in case of locally advanced disease, unresectable tumors, metastatic or recurrent disease has been encouraging [7].

Medical Management

The use of tyrosine kinase inhibitors in the management of GIST both in adjuvant and neo-adjuvant settings has been revolutional. National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant imatinib therapy to reduce tumor size before surgery and minimize morbidity in patients with primary GISTs considered unresectable or resectable with high-risk morbidity [12].

Imatinib is among the first of the drugs in this group. Initially used in chronic myeloid leukemia, its activity against receptor tyrosine kinases cKIT and PDGFRA is of importance in GIST [4]. The standard dose is 400 mg/day in adjuvant or metastatic settings. Improved response rates were documented for patients with exon 9–mutant tumors treated with imatinib 800 mg versus 400 mg (CR/PR, 67% vs 17%; p 0.02) [3, 15]. In the case of progressive disease, before sunitinib therapy, the drug dose may be increased to 800 mg/day. The NCCN 2012 guidelines recommend 1 year of adjuvant imatinib therapy in intermediate and high-risk GISTs. Also for GISTs at least 5 cm in size, 3 years of adjuvant imatinib should be given [16].

In the neoadjuvant setting, the duration of imatinib therapy should be to capture the window of opportunity between maximal tumor response and disease progression. In a study by Gold and Dematteo, surgery was encouraged within 6 months of initiating therapy [17], and based on another study by Bednarski et al., the time of surgery should not exceed 12 months [18]. The time to discontinue neoadjuvant treatment for surgery should be personalized to the individual patient [14].

The Choi criteria (Table 2) was used to assess radiological response in CT scan based on decrease in tumor size by 10% in any dimension or decrease in structure by 15% and was found to be more predictive of time to tumor progression [12, 13].The median time to disease progression on imatinib is approximately 2–3 years [3]. The most common adverse events include periorbital edema, fatigue, nausea, diarrhea, musculoskeletal pain, rash, anemia, and granulocytopenia [19].

In patients with progressive disease, the first step may be to escalate the dose of imatinib to 800 mg, provided the adverse effects are manageable. However patients with progression of disease despite long-term imatinib therapy, rapid increase in size of tumor in a short time while on imatinib or intolerant to imatinib should switch over to second-line agents like sunitinib [3, 19]. Sunitinib (37.5 or 25 mg/day) has significant antitumor and antiangiogenic activity since it targets KIT, PDGFR, vascular endothelial growth factor receptor (VEGFR), Fms-like tyrosine kinase 3 (FLT3), and RET. [3, 20] The most common adverse events include fatigue, diarrhea, skin discoloration, nausea, mucositis, hypertension,

Table 2 Criteria for assessment of response

Response	Description
Complete response (CR)	Disappearance of all lesions. No new lesion
Partial response (PR)	≥ 10% decrease in sum of long axis diameter of target lesions or
	≥ 15% decrease in tumor density on CT (HU) without evidence of new lesion or progression of non-measurable disease
Stable disease (SD)	Not satisfying CR, PR, or PD. No evidence of worsening symptoms due to tumor progression
Progressive disease (PD)	≥ 10% increase in sum of long axis diameter of target lesions, and not satisfying PR by tumor density decrease
	Appearance of new lesion
	New intratumoral nodule or worsening intratumoral nodule

The Choi criteria [13]

hand and foot syndrome (palmar–plantar erythrodysesthesia), impairment of left ventricular ejection fraction, and hypothyroidism [19].

Protocol-based therapies are started when patient develops sunitinib resistance. Regorafenib, an oral multikinase inhibitor of angiogenic (VEGFR-1,VEGFR-3, and TIE2), stromal (PDGFRB and FGFR) and oncogenic (KIT, RET, and BRAF) receptor tyrosine kinases, (64, 165, 196) has been recently approved in the third-line therapy after imatinib and sunitinib failure [19, 20].The most common grade 3 side effects were hypertension, hand-foot skin reaction, and diarrhea [3].

Many agents are under investigation to target KIT or KIT signaling (PI3K MEK) or other intracellular events (histone deacetylase inhibitors, heat shock protein, mTOR pathway). Also, newer TKIs are being looked upon in face of development of resistance like sorafenib, nilotininb, dasatinib, pazopanib for management of refractory GIST [19–21].

Surgical Management

Surgery is the treatment of choice for isolated GISTs without evidence of metastasis. The objectives of surgery include macroscopically complete resection while avoiding tumor rupture and injury to the pseudo-capsule along with microscopically negative margins [6]. Prophylactic lymphadenectomy is not indicated since it commonly disseminates via hematogenous route. Abdomen should be explored carefully during surgery to exclude the liver and peritoneal metastases. If the tumor is resectable, surgery may be radical, otherwise subsequent treatment with imatinib is given [4].

Modest surgery as wedge resection with 1–2 cm margin should be considered. Laparoscopic resection of GISTs is emerging as an alternative to traditional open approach with low recurrence rates, low morbidity, and shorter hospital stay [16]. In addition, combined laparoscopic and endoscopic techniques have become operational for managing GIST. Laparoscopic wedge resection (LWR), laparoscopic and endoscopic cooperative surgery (LECS), combined laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET), non-exposed endoscopic wall-inversion surgery (NEWS), laparoscopic assisted endoscopic full-thickness resection (LAEFR), endoscopic full thickness resection (EFTR), and endoscopic enucleation (which includes endoscopic submucosal dissection (ESD), endoscopic muscularis dissection (EMD), and endoscopic submucosal tunnel dissection (ESTD)) are among the recently used techniques [7, 12, 22, 23].

If the margin is macroscopically positive, a re-resection should be considered if the site(s) of positive margin can be located precisely, the residual tumor is completely resectable, dissemination or serosal invasion is not present, and morbidity is acceptably low. If the site(s) of positive margin is/are uncertain and/or there is high morbidity, the patient should be kept under observation. Microscopically, positive margins on final histopathological examination does not warrant re-operation [4, 5, 7].

Recurrence is common in case of incomplete resection of tumor (seen in up to 90% cases), which occurs usually 18–24 months from the time of the index procedure, and 5-year survival after resection of a localized tumor is ≈ 50% [4].

Urgent surgery may be required in settings when GISTs cause acute hemorrhage, perforation, or obstruction. Radical surgery may not be possible in such cases, and hence partial resection should be done followed by imatinib therapy. One should attempt to remove GIST if found incidentally during any surgical procedure [4].

Surveillance

High-risk patients generally have a tendency to recur within the first 2 years from the end of adjuvant therapy, whereas low-risk patients may relapse subsequently. The ESMO guidelines provide a standard postoperative protocol for follow-up of patients who have successfully undergone surgical resection of a primary GIST. For high-risk patients, CT scans of the abdomen and pelvis should be done every 3–

6 months during the first 3 years of adjuvant therapy. Regular follow-up is recommended every 3 months in the first 2 years, every 6 months until 5 years, and annually for an additional 5 years from the discontinuation of adjuvant drug treatment. Follow-up is suggested every 6–12 months for approximately 5 years in the low-risk cases [3, 7, 13].

Conclusion

GIST has been recognized as a separate entity in the past decade as a separate class of mesenchymal tumors predominantly expressing c-KIT gene protein. Recent advances in the understanding of GIST behavior have resulted in the classification of these tumors by their relative risk of malignancy. Endoscopy and EUS currently play a key role in the diagnosis of GISTs of the GI tract. With the use of TKIs, patient outcome has improved remarkably. Surgery remains the mainstay of management of localized, resectable, and nonmetastatic tumors [11]. Disease progression is likely in metastatic disease despite administration of TKIs. Novel approaches targeting pathways downstream of KIT and PDGFRA regardless of the specific mutational activation mechanisms, or affecting the oncoprotein stability, are under way to open further treatment options for managing gastrointestinal stromal tumors. Multidisciplinary approach involving endoscopist, pathologist, radiologist, medical oncologist, and surgeon is required for optimal management of GIST.

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