Chapter 5

Gastric GIST

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Abstract

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. The stomach is considered the most common site of GIST, and the most common histopathological type of GISTs is spindle cell. Mutational analysis may help in defining the management of GIST. Multiple stratification modules are available for the estimation of GISTs' prognosis. Surgery is considered the only curative option for GISTs. The discovery of KIT protein has allowed better identification of GISTs and has allowed creation of selective tyrosine kinase inhibitors which dramatically affected GIST management. Results of trials on neoadjuvant imatinib therapy are promising. Adjuvant imatinib therapy is recommended for 3 years and has proven to improve outcome in high-risk GISTs. New therapeutic agents are now available in case of imatinib resistance. Follow-up of patients with GISTs depends on the type of GIST.

Keywords: GIST, gastric GIST, imatinib, tyrosine kinase inhibitors, primary GIST, metastatic GIST, recurrent GIST, imatinib resistance, KIT, PDGFRA

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract (GIT) [1, 2]. All GISTs are considered to have some degree of malignant potential [3]. The most common site of GISTs is the stomach (60%) [4]. Other common sites are jejunum and ileum (30%), duodenum (5%), rectum (2–3%), colon (1–2%), and esophagus (<1%) [4].

It has been estimated that GISTs comprise about 18% of all sarcomas and 80% of mesenchymal tumors found in the GIT [5]. GIST's true incidence has been underestimated as they were usually misdiagnosed as leiomyomas, leiomyosarcomas, and leiomyoblastomas [6]. A study which used the Surveillance, Epidemiology and End Results (SEER) data from the National Cancer Institute, reported that the incidence of GIST has increased from 0.028 cases

per 100,000 in 1992 to 0.688 cases per 100,000 in 2002, which is a 25-fold increase in incidence. This increase occurred after the availability of diagnostic criteria, especially after the year 2000 [7]. In 1992, 93% of mesenchymal tumors of GIT were identified as smooth muscle neoplasm and 6% as GISTs. In 1995, Miettinen et al. [8] discovered that 70% of GIST are positive for CD34, a myeloid progenitor cell antigen. Furthermore, CD34 were also found in Schwann cell tumors and some smooth muscle tumors [6]. In the late 1990s, Hirota et al. [9] discovered that GIST expresses KIT (CD117), a receptor tyrosine kinase encoded by the proto-oncogene c-kit. Subsequent studies showed that mutations in c-KIT are present in 85–100% of GIST cases, but not in leiomyomas or leiomyosarcomas. These findings made a breakthrough in identifications and management of GISTs. In the SEER data published by Perez et al. [7], 82% of mesenchymal tumors of GIST were classified as GIST and 17% were classified as smooth muscle neoplasms in 2002, which shows how GISTs were poorly identified and were under-diagnosed [7]. GISTs appear to be more common in African Americans, Asians, and Pacific Islanders than in Caucasian patients, and men appear to have a slightly increased incidence [7, 10]. GISTs tend to be infrequent before the age of 30 and are most common after the age of 60 [7]. The median age of diagnosis is between 58 and 65 years [7, 10–13]. Two studies from Europe have shown that GIST incidence is about 1.1 cases/100,000/year [11, 14].

Though rare, GISTs can also affect the pediatric population. A study carried out by Miettinen et al. which included 1782 patients with gastric GIST, reported 44 cases under the age of 21 (2.6%) [15] with an age range from 5 to 21 and a median age of 14.5 years [15]. Prakash et al. [16] reported six cases of gastric GIST with a mean age of 12.8 and an age range from 10 to 18. Pediatric GISTs are commonly of epithelioid type, occur more in females, and have a higher incidence of multifocal presentation and lymph node metastasis. Pediatric GISTs also tend to lack a KIT or a platelet-derived growth factor receptor-α (PDGFRA) mutation [17, 18].

2. Risk factors

There are no known risk factors for GIST. Though most of GISTs are sporadic, the minority occur as part of hereditary syndrome.

Familial GIST syndrome: several family members with hereditary mutations in either the KIR or PDGFRA genes have been reported in the study [19–28]. These families have a higher risk to develop multiple gastric and small bowel GISTs. Some patients may have skin hyperpigmentation, dysphagia, gastrointestinal autonomic nerve tumors, intestinal fibromatosis, and inflammatory fibroid polyps [19–28].

Carney-Stratakis syndrome is an autosomal-dominant disease which is characterized by dyad of multifocal GISTs and paragangliomas [29]. Patients do not have KIT or PDGFRA mutations, but do have mutations of succinate dehydrogenase subunits (SDH) A, B, C, or D [30].

Carney's triad: a very rare non-heritable syndrome characterized by gastric GIST, paraganglioma and pulmonary chondromas. These patients are characterized by mutations succinate dehydrogenase subunit (SDH) C [29] but lack mutations of KIT and PDGFRA.

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Neurofibromatosis type 1: patients with NF1 are more predisposed for multifocal GISTs that mainly affect the small intestine [31].

3. Molecular biology

GISTs are characterized by mutations in KIT and PDGFRA genes that encode tyrosine kinase receptor type III [32].

3.1. KIT-mutant GIST

Though 95% of GISTs are positive for KIT, only 60–85% have mutations in KIT. The most common mutations encountered are mutations of exon 11 (juxtamembrane domain) [4] which is found in about two-thirds of GISTs. Exon 9 (extracellular domain) is less common (9–20%) and is principally correlated with GIST of the small bowel and has a greater malignant potential [4, 33].

3.2. PDGFRA-mutant GIST

About 5–10% of GISTs have PDGFRA mutations which have a tendency for localized gastric GIST and epithelioid type [4]. The most common type of mutation is the PDGFRA exon 18 mutation D842V, which is associated with imatinib resistance and has a lower risk of recurrence than GIST with KIT mutations as well as a more benign course 9 [34].

3.3. Wild-type GIST

Approximately 12–15% of adult GIST and 90% of pediatric GIST do not have KIT and PDGFRA mutations [33]. Wild-type (WT) GISTs comprise GISTs that arise in NF1, Carney-Stratakis syndrome, and Carney triad [4]. WT GISTs may have other forms of mutations. BRAF V600E substitution has been described in 7–13% of WT GISTs [35, 36]. About 30% of WT GISTs are SDH deficient and occur solely in the stomach. They mainly affect children and young adults and have a variation in their nature from being indolent to progressive [4].

4. Histopathology

The three main histopathologic subtypes of GIST are spindle cell, epithelioid, and mixed types, with spindle cell type being the most common constituting about 70% of GISTs, while the other two subtypes, epithelioid and mixed, are less common, accounting for 20 and 10% of all GISTS, respectively [6]. Epithelioid GIST is commonly observed in the stomach and omentum [6]. About 95% of GIST will be immunohistochemical positive for CD117(c-KIT) [4]. Epithelioid type has a weaker KIT positivity than spindle cell type [37]. In addition, 70–90% are positive for CD34, 20–30% for actin, 8–10% for S-100, and 2–4% for desmin [38]. DOG1 marker, also known as ANO1, has more than 95% sensitivity for GIST and is expressed in more than 35% of GISTs negative for c-kit [39, 40].

5. Clinical picture

About 60% of GISTs occur in the stomach, 30% in the jejunum and ileum, 5% in the duodenum, 2–3% in the rectum, 1–2% in the colon, and < 1% in the esophagus [4]. About 70% of GISTs are symptomatic, 20% are asymptomatic, and 10% are discovered at autopsy [41]. The main symptoms of GIST are GI bleeding, abdominal discomfort, and abdominal mass. GISTs are highly vascular tumors and may grow quickly and cause massive gastrointestinal or intraperitoneal hemorrhage [42]. Obstruction symptoms such as dysphagia, obstructive jaundice, and small bowel obstruction may also occur [42].

Extragastrointestinal GISTs occur in less than 10% of GISTs and mainly occur intra-abdominally and affect omentum and mesentery. Such tumors are considered more aggressive than gastric GIST and have a poorer prognosis similar to small bowel GISTs [43, 44].

About 50% of patients will present with metastatic disease with the most common site of metastasis being liver at about 65%. Other common metastatic sites are omentum and peritoneum. Extra-abdominal metastasis, lung bone, and lymph node metastasis are not common [13].

6. Prognosis

Various risk stratification models (**Table 1**) have been proposed that are based on site, size, mitotic index, and tumor rupture. Gastric GISTs are known to have better prognosis than non-gastric GIST [46].

Tumor rupture is known to be associated with a very high risk of GIST recurrence [47]. TNM staging is also available for GIST staging [48]. However, these stratification systems are not commonly used in clinical practice.

As an alternative to the risk classification systems that stratify patients into distinct groups, others have quantified the risk of disease recurrence after complete resection as a continuous variable through the use of a GIST nomogram that includes the disease site [49]. Different nomograms have been developed by others as well.

GIST nomograms [49, 50] have been used to assess the risk of disease recurrence after complete resection as a continuous variable instead of the risk stratification systems that stratify patients into separate groups. Recently, a new risk stratification system has been developed in which tumor size and mitotic counts were assessed as continuous, nonlinear variables, and prognostic contour maps were then generated based upon these data plus site and tumor rupture [51]. These prognostic contour maps resulting from nonlinear modeling are used for the assessment of individualized outcomes.

Deletion type of mutations affecting codons 557 and 558 in KIT gene is considered a risk factor for recurrence regardless of different classification systems [4].

Pfetin is a prognostic biomarker which is still under investigation with promising results. Lack of Pfetin expression seems to be associated with a higher GIST recurrence [52]. Orita et al. [52]

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Classification system	Prognostic criteria	Risk definition	Risk groups	Comments
NIH [6]	Tumor size Mitotic index	Aggressive behaviors of GISTs	Very low risk Low risk Intermediate risk High risk	Does not differentiate between malignant and benign tumors knowing the fact that even small-size tumors with a low mitotic count may metastasize Does not take GIST site into consideration
Modified NIH [45]	Tumor size Mitotic index Primary tumor site Tumor rupture	Risk of recurrence	Very low risk Low risk Intermediate risk High risk	Tumor location outside the stomach is a prognostic factor for survival independent of the mitotic count and tumor size
AFIP [46]	Tumor size Mitotic index location	Risk of recurrence	Very low risk Low risk Intermediate risk High risk	This classification considered a total area of 5 mm^2 in 50 fields HPF characterized by the use of different optical components, while in practice, 50 HPF typically corresponds to a total area of 10 mm^2 This classification is recommended by GEIS guidelines

Table 1. Different stratification systems for GISTs.

had 45 GIST cases, of which 37 were in the stomach. All GIST patients had R0 resection. There were seven recurrences with five recurrences being gastric GIST recurrences. Thirteen GIST patients were Pfetin negative and 5/13 Pfetin negative GISTs had recurrences [52].

7. Diagnostic evaluation

A computed tomography (CT) scan (**Figure 1a** and **b**) is considered the first imaging to be done to evaluate anatomic location, extension, and metastasis of GISTs. Oral and IV contrast should be given to delineate bowel margins. GISTs can display endophytic and exophytic growth, and large GISTs may appear heterogeneous due to focal areas of hemorrhage or necrosis [53]. Magnetic resonance imaging (MRI) is used to further evaluate liver metastasis or rectal GIST [54]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) is highly sensitive but not specific for GIST, and it is mainly useful to monitor response to tyrosine kinase inhibitors [55, 56].

Upper GI endoscopy may be useful for gastric GIST. Both GISTs and leiomyomas will appear as a submucosal mass with normal overlying mucosa and bulging into gastric lumen. Mucosal ulceration may occur. Endoscopic ultrasound (**Figure 2**) may not be useful, however, when combined with FNA sensitivity, and accuracy may reach 82 and 86%, respectively [57]. Routine biopsy is not needed routinely for local resectable gastric GISTs proved by imaging studies.

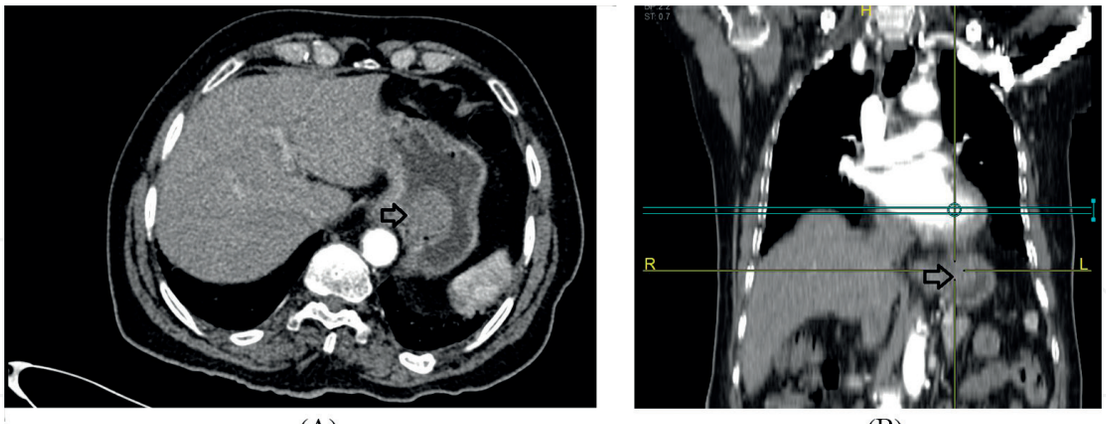

Figure 1. An axial (A) and coronal (B) CT image showing a well-defined mass lesion (arrow) in the anterior gastric wall in the proximal stomach measuring 2.9x2.5x2.7.

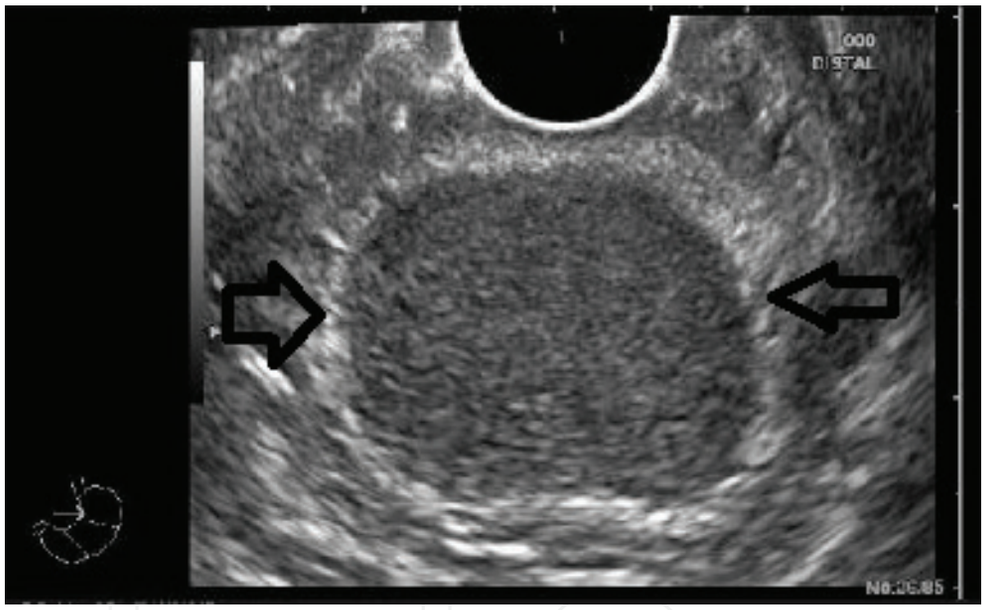

Figure 2. Gastric EUS showing a well-defined hypoechoic gastric submucosal lesion (between the two arrows) from the fourth layer of the stomach wall suggestive of GIST.

8. Management

Complete surgical resection is the recommendation of choice for localized GIST with a target of R0 resection with complete surgical removal of the tumor without disturbing the capsule [4]. Though surgery is considered the only curative option for GISTs, a multidisciplinary approach is needed for best medical and surgical management. Segmental resection of the stomach as wedge resection is accepted, and extensive resection is usually not needed. Lymphadenectomy is also not required as GISTs rarely metastasize to lymph nodes [4]. The discovery of KIT(CD117) (receptor tyrosine kinase) in GISTs has revolutionized GISTs management. Imatinib mesylate is a selective tyrosine kinase inhibitor that selectively inhibits KIT and had a significant impact on the prognosis of GISTs as will be discussed subsequently.

8.1. Management of primary resectable disease

8.1.1. Preoperative therapy for primary GISTs

There is still no consensus on the role of neoadjuvant imatinib therapy in resectable GISTs [4]. However, imatinib therapy might be considered for advanced or borderline resectable tumors. Multiple prospective and randomized trials have shown that neoadjuvant imatinib therapy (with a dose of 400 mg/day) in cases of advanced GIST will cause a reduction in tumor size and enable an R0 resection with an increased chance of organ preservation (**Table 2**). However, if KIT exon 9 mutation is detected and neoadjuvant therapy is planned, the dose may be increased to 800 mg per day as recommended by the European Society for Medical Oncology (ESMO) guidelines.

Study	Published year	Type of study	Type of patients assessed	Dose of imatinib given	Median follow-up	Primary end point	Results
RTOG (Radiation Therapy Oncology Group) 0132 [1, 116]	2009	Phase II prospective	1. Advanced primary GIST of >5 cm (Group A, 30 p) 2. Recurrent or metastatic tumors of ≥2 cm (group B, 22 p)	Neoadjuvant 600 mg/day for 8–12 weeks of treatment with a median of 65 days then 600 mg/day adjuvant therapy for 2 years	1. Group A 4.9 y 2. Group B 5.5 y	RFS	1. The 2-y estimated overall survival was 93.3 and 90.9% in Group A and Group B, respectively, with a median follow-up of 3 y 2. The 5-y PFS and OS were 57% in group A, 30% in group B, and 77% in group A, 68% in group B, respectively
McAufliffe et al. [117]	2009	Phase II randomized	Primary GIST Metastatic GIST of ≥1 cm 3. 19 patients involved	Neoadjuvant 600 mg/day given at 3, 5, or 7 days; then adjuvant 600 mg/day for 2 years	32 m	Tumor cell apoptosis	All patients had a radiographic response with 1 week of imatinib therapy. In addition, the rate of tumor cell apoptosis had a positive correlation duration of imatinib therapy where the maximum tumor cell apoptosis was seen with 7 days neoadjuvant imatinib therapy
APOLLON [118]	2012	Prospective open-label phase II	1. KIT or PDFRA positive GIST. Tumors had to be locally advanced, potentially resectable, and no metastasis 2. 45 patients involved	Neoadjuvant for 6 months 400 mg/day with no postoperative adjuvant therapy	36 m	Overall tumor response	1. R0 resection was achieved in 30/34 patients and PFS at 3 years was 85.2%. 2. Predicted operation was downsized with imatinib therapy

Study	Published year	Type of study	Type of patients assessed	Dose of imatinib given	Median follow-up	Primary end point	Results
Kurokawa et al. [59]	2017	Phase II prospective	1. Primary GISTs in the stomach with tumor size of ≥10 cm with no metastasis 2. 53 patients enrolled	1. Neoadjuvant 400 mg/day for 6 months 2. Adjuvant 400 mg/day for at least 1 year	32 m	R0 resection rate	1. The R0 resection was achieved in 91% of patients (48/53) and at least half of the stomach was spared in 42/48 patients who had R0 resection. 2. After R0 resection, all patients received imatinib 400 mg/day for at least 1 year. The 2-year OS and PFS were 98 and 89%, respectively

RFS, recurrence-free survival; OS, overall survival; y, years; m, months.

Table 2. Summary of studies assessing the role of neoadjuvant imatinib in treatment of GIST.

8.1.2. Surgery for primary GISTs

Surgical resection with negative margins is the recommended treatment for localized primary GISTs and is the only curative treatment for GIST [58, 59]. A published study that contained 200 GIST patients [13] with 46.5% of the cases being primary local GISTs and 39% of the cases gastric GIST, which was the most common type, reported that complete resection was achieved in 80 patients (86%) with primary disease, and those patients had a 54% of a 5-year survival rate with a median survival of 66 months, while patients with incompletely resected or unresectable disease had a median survival of 22 months. Complete resection of even a locally advanced disease is associated with improved survival [60].

Surgical resection is recommended for GISTs with a size of 2 cm or more [61]. However, there is still no consensus on the management of GIST less than 2 cm [62, 63]. Multiple studies have reported the occurrence of microscopic gastric GIST [64–67]. Agaimy et al. [68] discovered microscopic GISTs in 22.5% of consecutive autopsies for adults of >50 years old with all lesions detected in cardia, fundus, and proximal body. Kawanowa et al. [67] reported 35% of microscopic GISTs in patients who had gastric resection for stomach cancer. Ninety percent of these microscopic GISTs were in the upper body.

GISTs have been reported as an incidental finding discovered by routine OGDs and in gastric specimens post sleeve gastrectomy [69, 70] and have caused a dilemma about whether routine preoperative gastroscopy should be done before each bariatric procedure to avoid missing such incidental tumors [70]. Sepe et al. [71] had developed an algorithmic approach for gastric GIST which was adopted by The National Comprehensive Cancer Network (NCCN). They proposed that GISTs with no high-risk EUS features (irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity) can be followed up by EUS. NCCN adopted this approach and suggested that EUS surveillance every 6–12 months may be done for GISTs of <2 cm with no high-risk features [72].

Endoscopic resection of gastric small submucosal tumors is a promising technique with a favorable outcome. Andalib et al. [73] described endoscopic resection of 12 cases with gastric GISTs arising from muscularis propria with an average size of 2.4 cm and no complications of bleeding or perforation. However, 50% of cases had positive microscopic margins but there is no evidence that a positive microscopic margin after macroscopic resection requires re-excision [74], and with an average follow-up of 12 months, none of the patients had recurrence. Zhou et al. [75] described endoscopic resection of 26 cases of gastric submucosal tumors, out of which 16 were gastric GISTs. The mean tumor size was 2.8 cm and all of the tumors were resected completely without interruption of capsule. None of the patients had severe complications as bleeding perforation or abdominal abscess [75]. No recurrence was found with a mean follow-up of 8 months. Nevertheless, tumor spillage and perforation after endoscopic resection had been described [76], and the technique needs to be validated by prospective multicenter trials and cannot be routinely recommended.

As mentioned before, surgery is the main and only curative option for primary localized resectable GISTs [77]. The primary technical goal of surgery is complete macroscopic resection with an intact pseudocapsule and a negative microscopic margin (R0 resection) [77]. Routine lymphadenectomy is not needed as adult GISTs rarely metastasize to lymph nodes [78]. Pediatric GISTs, however, have a higher incidence of lymph node metastasis [78] and lymphadenectomy may be needed for this population [79, 80].

Wedge resection with negative margins is the usual treatment for gastric GISTs [81] unless the tumor is found invading the surrounding tissues where en bloc resection of involved surrounding organs may be appropriate [81]. Patients with low-grade tumors may have a 5-year survival up to 80%. It is still important to avoid tumor rupture and spillage, as this is associated with an increased risk of recurrence and low survival rates [47, 60]. The role of laparoscopy in gastric GISTs is developing with promising outcomes. Two meta-analysis studies have concluded that, when compared to open, laparoscopy seems to result in shorter hospital stays with no difference in operative time, adverse events, estimated blood loss, margin positivity, or overall survival (OS) and recurrence rates [82, 83]. Current NCCN guidelines [84] recommend that a laparoscopic wedge resection for gastric GISTs of 5 cm or less is appropriate and tumor resection may be done using a laparoscopic or a laparoscopic-assisted technique with hand port for GISTs more than 5 cm.

8.1.3. Adjuvant therapy for primary GISTs

Unlike neoadjuvant imatinib therapy, the role of adjuvant imatinib therapy is better established. Recurrence rates of 50% have been reported in localized GISTs that have been completely resected [4]. Multiple randomized trials have proven the efficacy of adjuvant imatinib.

The first randomized phase II trial done on the role of adjuvant imatinib was The American College of Surgeons Oncology Group (ACOSOG) trial Z9000 [85] which assessed the role of adjuvant imatinib dose of 400 mg/day for 1 year for patients with a high-risk GIST. High risk was defined in this study as a tumor diameter of >10 cm, intraperitoneal tumor rupture, or up to four peritoneal implants. The study involved 106 patients with GISTs, 50% of the cases were gastric GISTs. After a median follow-up of 7.7 years, the 1-, 3-, and 5-year overall survivals (OS) were 99, 97, and 83%, respectively, which is much better than historical controls (35%) [85]. The 1-, 3-, and 5-year RFS rates were 96, 60, and 40%, respectively. Recurrence free survival (RFS) was lower with a larger tumor size, KIT exon 9 mutation, a high mitotic rate,

and older age. They concluded that adjuvant imatinib for 1 year prolongs RFS and OS, but the optimal duration of adjuvant imatinib was still to be decided.

Three phase III trials have assessed the efficacy of adjuvant imatinib, ACOSOG Z9001 [86], SSG XVIII trials [87], and EORTC 62024 [88]. Only ACOSOG Z9001and EORTC 62024 had no treatment control arm. The American College of Surgeons Oncology Group (ACOSOG) trial Z9001 [86] is the first randomized phase III, double-blinded, placebo-controlled, multicenter trial done regarding the role of adjuvant imatinib therapy. A total of 359 patients were randomized to receive imatinib 400 mg/day for 1 year, and 354 patients were randomized to receive placebo for 1 year following surgical resection of the tumor. The trial reported that imatinib therapy significantly prolonged RFS when compared to placebo (98 versus 83%) in all risk categories (based upon size, mitotic rate, and location in the GI tract) [86]. Overall survival was similar at 1 year with 99.2 versus 99.7%, and imatinib therapy was tolerated with low side effects. The trial planned a minimum follow-up of 3 years for the patients but it was stopped early with a shorter median follow-up of 19.7 months. The lack of difference in overall survival in this trial may be explained by a short duration follow-up, a limited number of relapses, and a high degree of efficacy of imatinib in relapsed disease [89]. As a result of this study, The U.S. Food and Drug Administration approved adjuvant imatinib in the adjuvant setting by the U.S. Food and Drug Administration for GISTs of ≥3 cm, without guidance as to the optimal duration of treatment or which patients are most likely to benefit. The long-term results of this study were published with a median follow-up of 74 months with no difference in the 5-year RFS and OS.

Another phase III prospective, randomized, open-label trial was done by The Scandinavian Sarcoma Group (SSG) XVIII [87]. This trial compared 36 versus 12 months therapy of adjuvant imatinib (400 mg daily) in 400 patients with a high-risk-resected GIST with a median follow-up of 54 months. A high-risk GIST was defined as a tumor size of >10 cm, a mitotic count of >10/50 high-power fields (HPF), a tumor size of >5 cm with a mitotic rate of >5/HPF, or a tumor rupture. About 50% of the patients had gastric GIST in this study. The study reported prolonged 5-year RFS and OS rates for patients assigned for 36 months imatinib adjuvant therapy compared with patients assigned for the 12-month group, 65.6 versus 47.9% and 92% versus 81.7%, respectively. The results of this trial resulted in NCCN guidelines recommending adjuvant imatinib for at least 3 years for patients with intermediate or high risk of GIST recurrence [90]. In a latter follow-up report for the Scandinavian trial with a median follow-up of 90 months, patients assigned to a 3-year group had a persistent favorable outcome with significantly greater RFS (71 versus 52% and overall survival (92 versus 85%) [91].

The EORTC 62024 trial [88] is a phase III open-label randomized trial which assessed the efficacy of adjuvant imatinib for 2 years in localized surgically resected high- or intermediate-risk GISTs [88]. After surgical resection, 908 patients were randomized to either receive 2 years of imatinib 400 mg/day or observation alone. After a median follow-up of 4.7 years, RFS at 3 years was 84% in imatinib group versus 66% in control group and 69 versus 63% at 5 years ($P < 0.001$). No difference was detected in a 5-year OS. The 5-year imatinib failure-free survival (IFFS, the time to death or starting a TKI other than imatinib) was 87% in imatinib group and 84% in control group ($P = 0.23$). Among patients with a high-risk GIST (528 patients), there was a trend favoring adjuvant imatinib ($P = 0.087$).

As a result of the findings of the previous trials, both NCCN and ESMO guidelines as well as consensus of the scientific community recommend 3 years of adjuvant treatment with imatinib

in high-risk patients [4]. By contrast, adjuvant therapy is not needed in low-risk patients, and there are no sufficient data to support adjuvant imatinib therapy in intermediate-risk patients [4]. Whether doses higher than 400 mg/day should be used is still questionable. Moreover, whether the imatinib dose should be continued more than 3 years is not known. A single-arm phase II 5-year adjuvant imatinib trial, PERSIST5, has completed its accrual, and still survival data reports are pending. Whether patients who had R1 resection for their GISTs should receive adjuvant imatinib is also not clear as there are no data to support adjuvant imatinib therapy in such cases. Re-excision may be appropriate in these situations.

8.2. Management of metastatic and recurrent GIST

GISTs mostly recur in the first 5 years after surgical resection, while less recurrence is observed after 10 years [92]. A study, with pooled analysis from 10 series and included 1625 patients, reported that 5-year, 10-year, and 15-year RFS were 70.5, 62.9, and 59.9%, respectively [92]. It was observed that the larger the size of the tumor, the higher the risk of recurrence. Compared with tumors of <1.1 cm in size, tumors with sizes of 1.1–2, 2.1–5, 5.1–10.0, 10.1–15.0, and > 15 cm were associated with a hazard ratio (HR) of 2.19, 4.45, 21.56, and 27.98, respectively. There was also a positive correlation between tumor mitosis rates and risk of recurrence. Compared with tumors with a very low mitosis count (<2/50 HPF), tumors with a low count (2–5/50 HPF), a moderate count (6–10/50 HPF), and a high count (>10/50 HPF) were associated with HR of 3.78, 11.1, and 22.09, respectively. Gastric GISTs had better RFS than other types of GISTs. Tumor rupture was associated with a worse prognosis. About two-third and half of patients with recurrence had liver metastasis and peritoneal disease, respectively [93].

Patients with advanced (primary unresectable or metastatic GIST) are treated initially with imatinib rather than surgery.

A phase III randomized trail (EU-AUS trial) [94] included 946 patients randomized to either receive imatinib once or twice daily. At a median follow-up of 760 days, the trial reported that 56% of 473 patients receiving imatinib 400 mg/day had progressed while 50% (235) of 473 patients assigned to imatinib 400 twice/day had progressed. OS was 69 and 74%, respectively. There was no significant difference in response rates between the two groups. The study concluded that, although a daily dose of 400 mg of imatinib is enough, a dose of 400 mg twice daily significantly prolongs PFS.

In a phase II open-label multicentric randomized trial, B2222 study, which included 147 patients with advanced GIST, 73 patients received imatinib 400 mg/day and 74 patients received imatinib 600 mg/day. The study reported equal response rates, median progression-free survival, and median overall survival among both groups with a median survival of 57 months for all patients. No advantage was seen with using a higher dose of imatinib (600 mg/day) in this study. This study was followed by another phase III open-label multicentric randomized trial, S0033 study [95], which compared imatinib dose 400 mg/day to imatinib dose 400/mg twice daily. The study included 746 patients with advanced GIST with a median follow-up of 4.5 years. Similar findings were found with no statistically significant difference in response rates, PFS, or OS between either doses of imatinib. However, after progression on imatinib dose of 400 mg/day, 33% of the patients who were crossed over to receive a higher imatinib dose 400 mg twice daily achieved either an objective response or a stable disease [95].

Further analysis of data from EU-AUS and S0033 trials reported that tumor genotype has a significant prognostic impact on PFS and OS, with tumors with mutation of KIT exon 9 having a worse prognosis when compared to tumors with mutation of KIT exon 11 [96, 97].

A subsequent meta-analysis combining S0033 and EU-AUS trials [98] reported a minor albeit significant PFS advantage for a higher imatinib dose of 400 mg twice daily for patients with advanced GIST. The PFS benefit was only evident in patients with KIT exon 9 mutations treated with a high-dose imatinib without difference in OS between the two groups, while patients with KIT exon 11 had a more favorable prognosis. Thus, genotype is required for the treatment of advanced or metastatic GISTs.

The findings of the results of the previous studies [94, 95, 98] designated imatinib dosage of 400 mg/day to be the standard treatment for patients with advanced GISTs, and patients with advanced GISTs with KIT exon 9 mutations to be started on the higher imatinib dose (400 mg twice daily), keeping in mind that the toxicity of imatinib is dose-dependent [99]. Imatinib treatment should be life long as interruption of treatment has a higher rate of disease progression as proven by the phase III randomized trial [100–102]. Indications of surgery in advanced GISTs are still debatable. Multiple retrospective studies have shown that debulking surgery may be beneficial in patients with a stable disease without generalized progression as surgery may improve the prognosis. However, patients should be treated with imatinib first before attempting surgery [103–108].

8.3. Alternatives of imatinib in case of resistance or progression of disease with imatinib therapy

Most patients with advanced GISTs will show improvement with imatinib therapy, although a subgroup of patients will fail to show a response. Resistance to imatinib may be primary or secondary. Primary resistance is defined as continuous growth or growth within 6 months of therapy, and occurs in 15–20% of patients with advanced GIST [109] and occurs frequently in patients with wild-type (WT) GIST or KIT exon 9 mutations or D842V mutation in PDGFRA exon 18 [110]. Unfortunately, most patients develop secondary resistance, which is defined as patients who received treatment with imatinib for longer than 6 months and had an initial response and then developed progressive disease. Secondary KIT mutations occur frequently in KIT exons 13, 14, and 17 and a D842V mutation in PDGFRA exon 18 [111–113].

If a patient develops resistance, escalating imatinib dosage to 800 mg daily or shifting to a second-line therapy like sunitinib may be recommended.

Sunitinib is considered a second-line therapy for patients with advanced GIST refractory to imatinib therapy. Outcomes of a randomized phase III trial versus placebo reported a prolongation of the time to progression from 1.5 to 6.3 months in patients with GIST who progressed on imatinib treatment [114]. It is approved by the EMA and the FDA for the treatment of patients with GIST resistant to imatinib therapy and for patients who are not tolerant to imatinib therapy.

In case of progression on imatinib and sunitinib, regorafenib is considered a third-line therapy [4]. It was recently approved by EMA and FDA for the treatment of patients with unresectable or metastatic GISTs who are resistant or intolerant to imatinib and sunitinib, and

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it was tested in a phase III randomized trial which included patients with advanced GIST who progressed after imatinib and sunitinib failed. The study reported that regorafenib, when compared to placebo, has significant improvement in PFS [115]. Inadequate data are available for the efficacy of other tyrosine kinase inhibitors (e.g., sorafenib, pazopanib, and ponatinib) for imatinib and sunitinib refractory GISTs [4].

9. Follow-up

There are no studies assessing the efficacy of different follow-up modules. Nevertheless, follow-up strategies were created based on the fact that most recurrences occur within the first 5 years after surgery.

A follow-up schedule frequency is based on the risk of aggressiveness and recurrence of GISTs [4]. CT is favored over other imagings, such as MRI and FDG-PET scan, because it is more readily obtainable, although other modalities can be used in case CT is inconclusive.

9.1. Follow-up for localized resectable GISTs

Very low-risk patients with surgically removed tumor do not require a follow-up. Low-risk patients require an annual CT. Intermediate- and high-risk patients require CT every 4 months for the first 1–2 years, every 6 months for 3–5 years, and then CT every year thereafter [4].

9.2. Follow-up for unresectable/metastatic GISTs

Follow-up should be done at the start of every 3 months and can be delayed to every 6 months if there is response to the treatment.

10. Conclusion

Surgery is the only curative option for GISTs. The discovery of KIT protein had allowed the development of tyrosine kinase inhibitors which considerably affected the diagnosis and management of GISTs. A multidisciplinary approach is required for optimal management. Neoadjuvant imatinib therapy has produced favorable results so far; however, more studies are needed to define the optimal dose and duration of imatinib therapy. Adjuvant imatinib therapy for 3 years improves outcome in patients with high risk. Mutational analysis has an important role in the management of GISTs. New therapeutic agents have been developed for patients with imatinib resistance.

Conflict of interest

The author declares that there is no conflict of interest.

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