



Review Article



# Primary Hepatic Extra-gastrointestinal Stromal Tumors: Molecular Pathogenesis, Immunohistopathology, and Treatment

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## Abstract

Gastrointestinal stromal tumors are the most common mesenchymal tumors of the gastrointestinal tract. They originate from the interstitial cells of Cajal and are usually found in extrahepatic gastrointestinal sites. However, a small subset are derived from the liver and are known as primary hepatic gastrointestinal stromal tumors (PHGIST). They have a poor prognosis and are historically difficult to diagnose. Our objective was to review and update the latest evidence-based knowledge concerning PHGIST, with a focus on epidemiology, etiology, pathophysiology, clinical presentation, histopathology, and treatment. These tumors are usually found incidentally, occur sporadically, and are associated with mutations of KIT and PDGFRA genes. PHGIST is a diagnosis of exclusion, as it has the same molecular, immunochemistry and histological appearance as gastrointestinal stromal tumors (GIST). Thus, imaging, such as positron emission tomography-computed tomography (PET-CT) must be used to rule out metastatic GIST before a diagnosis can be made. However, with mutation analysis and pharmacological advances, tyrosine kinase inhibitors are typically pursued with or without surgical intervention. Other potential treatments include transcatheter arterial chemoembolization and tumor ablation. However, these are typically considered palliative options. As there are only a limited number of publications regarding PHGIST, data concerning morbidity and mortality are not yet available. Im-

munochemistry can help develop screening guidelines and evaluating resistance to treatment.

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## Introduction

Primary hepatic gastrointestinal tumor (PHGIST) is a rare type of mesenchymal tumor that is considered a subset of primary extra-gastrointestinal stromal tumors (extra-GIST).<sup>1</sup> Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract, comprising 2.2%. They frequently metastasize outside the GI tract.<sup>1,2</sup> Although reported cases of primary extra-GIST are increasing, the estimated prevalence of PHGIST is unknown because of the rarity of the disease.<sup>3</sup> Obtaining an accurate diagnosis of PHGIST is challenging, as symptoms are nonspecific and there are no unique identifiable radiological features. Immunochemical results are similar to those of GIST from other locations. These tumors are usually found incidentally, but are considered high risk because of the overall poor prognosis of gastric and small intestinal GIST.<sup>1</sup> Patients should be evaluated and treated even if asymptomatic. This review updates the latest evidence-based knowledge concerning primary hepatic GIST with a focus on epidemiology, etiology, clinical presentation, histopathology, and treatment.

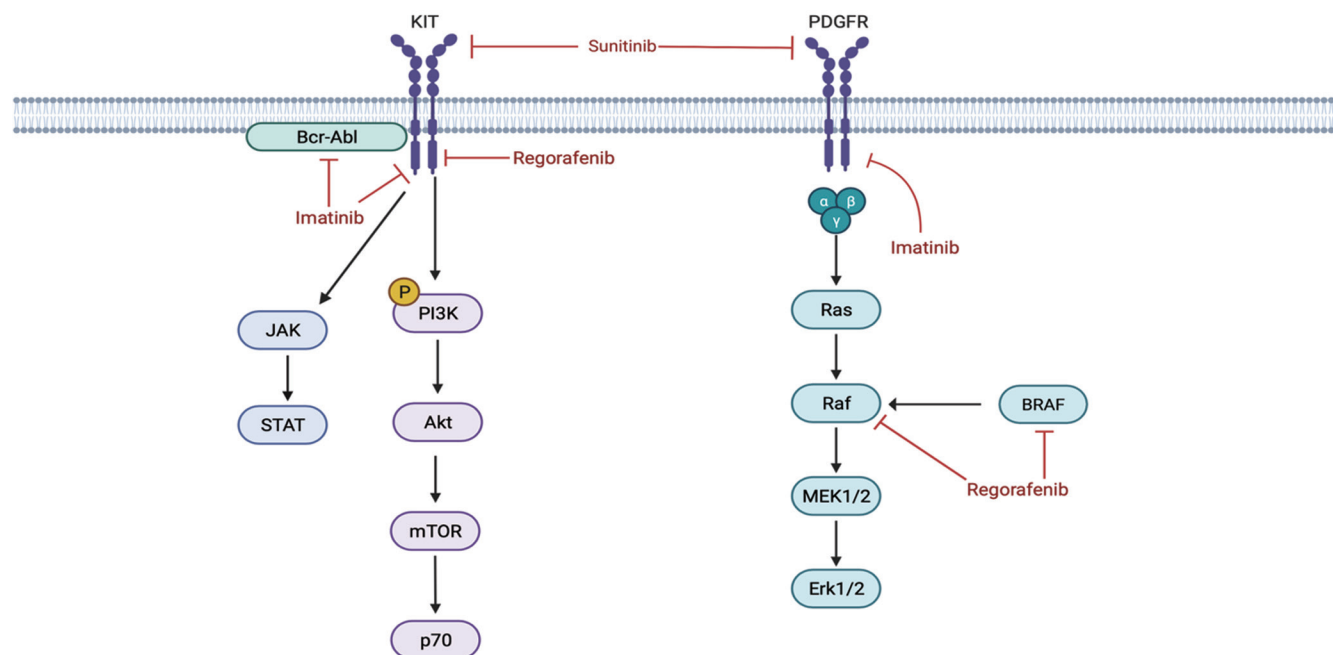
## Epidemiology

GIST most frequently occurs within the stomach (60–70%), followed by the small intestine (20–25%), colon and rectum (5%), and esophagus (<5%).<sup>4</sup> GIST represents 2.2% of all GI tumors.<sup>2</sup> However, primary extra-GIST are uncommon and account for <1% of GIST tumors, and PHGIST accounts for even fewer.<sup>1</sup> Only about 40 cases of PHGIST have been reported in the literature.<sup>4</sup> Patients were 17–79 years of age with an average age of 56 years. Most studies reported no sex predilection, but one found that GIST and PHGIST may have a male predilection.<sup>5</sup> Higher rates of PHGIST have been reported in China and Japan, with 1–2 cases each in Spain, the USA, Chile, France, Italy, India, and Korea.<sup>4</sup> Other than

**Keywords:** Primary hepatic gastrointestinal stromal tumor; Gastrointestinal tumor; Extra-gastrointestinal stromal tumor; Primary gastrointestinal stromal tumor of the liver.

**Abbreviations:** BRAF, v-raf murine sarcoma viral oncogene homolog B1; CD-117, cluster of differentiation 117; CD-34, cluster of differentiation 34; CEMRI, contrast-enhanced magnetic resonance imaging; c-KIT/KIT, cellular kinase, tyrosine; ECOG, Eastern Cooperative Oncology Group; extra-GIST, extra-gastrointestinal stromal tumor; FLT3, fms-like tyrosine kinase 3; HCC, hepatocellular cancer; ICC, interstitial cell of Cajal; ICLCs, interstitial Cajal-like cells; IORFA, intraoperative radiofrequency ablation; NF1, neurofibromatosis type 1; NRAS, neuroblastoma reticular activating system; OS, overall survival; PHGIST, primary hepatic gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; PET-CT, positron emission tomography-computed tomography; RET, rearranged during transfection; RFA, radiofrequency ablation; RFS, prolonged relapse-free survival; SDH, succinate dehydrogenase complex; TACE, transcatheter arterial chemoembolization; TAE, transarterial embolization; TKI, tyrosine kinase receptor inhibitor; VEGFRs, vascular endothelial growth factor receptor.

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**Fig. 1. Mechanisms by which of tyrosine kinase inhibitors regulate activation of PHGIST cells.** Receptor tyrosine kinases are a group of transmembrane tyrosine kinases involved in regulation of a wide range of complex cellular processes including growth, differentiation, and metabolism. One member of the family, KIT, can activate the JAK/STAT pathway which promotes cell proliferation, differentiation, and apoptosis. Another member, PDGFR, activates Ras/Raf pathway which leads to gene amplification and cell survival as well as apoptosis. Imatinib inhibits KIT, PDGFR(A), and Bcr-Abl. Sunitinib inhibits KIT and PDGFR(A). Regorafenib inhibits KIT, Raf, and BRAF. (Created in biorender.com.) Akt, protein kinase B; Bcr-Abl, breakpoint cluster region-Abelson proto-oncogene; BRAF, v-raf murine sarcoma viral oncogene homolog B1; Erk 1/2, extracellular signal-regulated kinase; JAK, janus kinase; KIT, tyrosine kinase; MEK 1/2, mitogen activated protein kinase kinase; mTOR, mechanistic target of rapamycin; p70, protein 70; PDGFR, platelet-derived growth factor receptor; PDGFR(A), platelet-derived growth factor receptor alpha; PHGIST, primary hepatic gastrointestinal stromal tumors; PI3K, phosphatidylinositol-3 kinase; Ras, rat sarcoma; Raf, rapidly accelerated fibrosarcoma; STAT, signal transducer and activator of transcription.

non-modifiable risk factors, such as age, sex, ethnicity, and inherited genetic syndromes, there are no known modifiable risk factors.

## Etiology

GIST originates from interstitial cells of Cajal (ICCs), the pacemakers for GI peristalsis. ICCs are most commonly found in the stomach, small intestine, colon/rectum, and esophagus.<sup>6</sup> When these same types of cells are found outside the GI tract, they are known as ICLCs (interstitial Cajal-like cells). Extra-GIST originates from ICLCs, and has been found in the upper and lower urinary tract, blood vessels, uterus, myocardium, and myometrium.<sup>6,7</sup> ICLCs have been identified within the periphery of the hepatic lobules and within portal spaces and septa.<sup>7</sup>

While the origin of PHGIST is still debated, two hypotheses have been proposed. One is that PHGISTs originate from ICLCs. This is supported by the finding that ICLCs are within the organs and vasculature outside the digestive tract, such as a single precursor human embryonic liver cells.<sup>4</sup> An alternative theory suggests that PHGISTs originate from undifferentiated mesenchymal stem cells located outside the GI tract that differentiate into ICLCs.<sup>4</sup> GIST may originate from stem cells that can differentiate into mesenchymal cells.<sup>4</sup> As PHGIST occurs within all lobes of the liver, it is thought that ICLCs are widespread within the liver.

The function and structure of ICLCs are similar to those of fibroblast-like ICC found near the myenteric plexus rather than ICCs with myoid features.<sup>8</sup> The physiological role of ICLCs in organs without pacemaker function leads is unclear.

It is also unknown how ICCs or ICLCs develop into tumor cells, but mutations likely play a role. Both GISTs, and ICCs are positive for KIT and CD34, and ICCs are the only cells in the GI tract positive for both KIT and CD34. Thus, GISTs are thought to originate from ICCs.<sup>9</sup> In 2008, Hinescu *et al.*<sup>10</sup> reported that ICLCs in rat mesentery were positive for KIT and CD34. However, at this time, no documentation regarding KIT and CD34 positivity in human mesentery ICLCs has been published. GIST mutations in KIT, platelet-derived growth factor receptor alpha (PDGFRA), HRAS, NRAS, BRAF, neurofibromatosis type 1 (NF1), or succinate dehydrogenase complex (SDH) have been reported.<sup>11</sup> The most common of these are gain-of-function mutations in KIT and PDGFRA genes, which occur in about 82–87% of mutations.

*KIT* and *PDGFRA* genes are located on 4q12 encoding type III receptor tyrosine kinase. KIT then activates PI3K/AKT/mTOR and JAK/STAT pathways. PDGFRA activates the RAS/MAPK kinase signaling pathways, which affect cell proliferation, differentiation, migration, apoptosis, and survival (Fig. 1). Mutations are clinically significant, as they influence treatment options with tyrosine kinase inhibitors. Mutation testing for c-KIT and PDGFRA is important because mutations on those genes are associated with resistance to tyrosine kinase inhibitors, in which case, other treatment modalities should be considered.<sup>12</sup> Understanding the mutations also helps differentiate between familial associations and primary tumor sites. For instance, NF1-GISTs are predominantly located in the small intestine, Carney-Stratakis syndrome, and Carney triad (mutations in SDH genes) are associated with gastric GIST, and familial GIST (*KIT* and *PDGFRA* genes) are associated with multiple GISTs in the GI tract.<sup>11,12</sup> PHGIST is

considered sporadic and has not been reported with familial GISTs or germ-line mutations.

### Clinical presentation

The clinical presentation of PHGIST is commonly nonspecific and includes shortness of breath, abdominal discomfort and pain, abdominal fullness and distention, nausea, decreased appetite, and weight loss (Supplementary Table 1).<sup>8</sup> Patients may be asymptomatic due to a lack of mucosal connection and deeper location.<sup>8</sup> Tumors can grow very large before becoming symptomatic.<sup>4</sup> Therefore, clinical symptoms vary concerning tumor size and location.<sup>5</sup>

### Pathology

PHGISTs are risk-stratified using the same classification guideline established for GIST by the National Institutes of Health (NIH), which includes classification from low to high risk based on tumor size, mitotic rate, and location to determine the best approach for treatment and prognosis.<sup>4</sup> Almost all PHGISTs are at high risk for mortality and are thought to have worse prognoses than GISTs.<sup>4</sup> NIH risk stratification is significantly different ( $p < 0.05$ ) when hepatic GIST is compared to other extra-GIST.<sup>2</sup> For example, when 23 hepatic GISTs were compared with 356 extra-GISTs, it was determined that hepatic GISTs were significantly larger, had a higher mitotic index, and higher risk ( $p < 0.05$ ).<sup>2</sup> In 2006, Liu *et al.*<sup>2</sup> reported 11 cases of PHGIST with a 5-year median disease-free survival of 24 months, and a 5-year disease-specific survival rate of 33%. Two of the patients had recurrent PHGIST and two had metastatic GIST.<sup>2</sup> The survival outcomes of GIST were much better. The estimated 5- and 15-year recurrent free survival rates for GISTs treated with surgery alone were 70.5% and 59%, respectively.<sup>13</sup> Because of the rarity of PHGIST, it is difficult to determine disease progression and survival time compared with GIST.

A review of single case reports found that 23 of 30 patients with PHGIST who received local hepatectomy alone or with chemotherapy had a survival rate of more than 6 months.<sup>4</sup> Although long-term prognostic data are not available because of the limited number of cases, it is thought that patients may have similar survival rates compared to patients with GIST when treated with chemotherapy.<sup>4</sup> Patients with GIST treated with chemotherapy had a 2-year progression-free survival rate of 77%, at which point the rate of secondary resistance mutations increased significantly to about 88% of patients. The longest reported living survivor died 22 years after initial diagnosis, 21 years after liver transplantation, and 9 years after recurrence with chemotherapy.<sup>14</sup>

Clinical presentation can also vary if primary hepatic GIST has metastasized. There are case reports of metastasis to the hepatic hilar lymph node, gastric, lung, brain, and bone.<sup>5</sup> Hu *et al.*<sup>15</sup> described a patient who developed shortness of breath with sharp pleuritic chest pain radiating to the right shoulder and who was diagnosed with a right hepatic lobe mass, which was positive for CD117. She had refused post-operative chemotherapy and 16 months later was found to have a hepatic hilar lymph node originating from PHGIST as no other primary site was located on imaging. Unfortunately, the other cases, which described metastatic PHGIST, did not describe the symptoms on presentation.

### Diagnostic imaging methods and findings

As GIST commonly metastasizes to the liver, metastatic GIST

must be ruled out order to diagnose PHGIST. Differentials for PHGIST are broad and include, but are not limited to, hepatocellular carcinoma, hepatic hemangioma, hepatic adenoma, focal nodular hyperplasia, hepatic abscesses, lymphoma, and hepatic non-GIST metastases. PHGIST does not have specific radiological features. Therefore, it is commonly misdiagnosed.<sup>4</sup> Modalities for imaging include CT enterography, abdominal ultrasound, MRI, and PET/CT combination therapy. The advantages and disadvantages of each should be considered, and sometimes more than one imaging modality is necessary.

On MRI, PHGIST usually appears as a round cyst-like solid mass that can be lobulated with bright or fuzzy borders and a thick pseudocapsule with central necrosis and cysts.<sup>4</sup> However, Mu *et al.*<sup>16</sup> reported that the capsule or pseudocapsule of PHGIST tends to enhance unevenly during the arterial phase. Ring augmentation paired with cystic alterations can readily be mistaken for hepatoseptoma, especially when minor septations on the border resemble abscess chambers. PHGIST, has also been reported to have features similar to hepatocellular cancer (HCC) with necrosis. However, the degree of enhancement has been described as not much greater than that of the normal liver. PHGIST enhancement in the venous phase is lower than or comparable to that in normal liver tissues. Mu *et al.*<sup>16</sup> reported a biopsy-confirmed PHGIST patient had a mass with hypointensity on the T1-weighted pictures and hyperintensity on the T2-weighted images with limited diffusion on contrast-enhanced magnetic resonance imaging (CEMRI) and central necrosis and capsule ring enhancement. Thus, CEMRI features including arterial phase hyperenhancement, capsule enhancement, washout, and bleeding on imaging, can result in confusion with HCC. Therefore, PHGIST should be considered in the differential when imaging appears consistent with HCC.

No morphological, immunohistochemical, or molecular characteristics distinguish PHGISTs from metastatic GIST or other E-GISTs. However, metabolic imaging such as PET-CT (positron emission tomography-computed tomography) can help differentiate PHGIST from metastatic GIST and E-GIST by ruling out additional tumor sites.<sup>4</sup> PET-CT is currently the best method to exclude PHGIST from extrahepatic lesions and is considered the most sensitive method for diagnosis, evaluating potential treatment, and efficacy of drug therapy. Tumor markers can be supportive, but are not diagnostic. Previous case reports have documented that alpha-fetoprotein, CA19-9, and CA125 levels may be high or normal.<sup>4</sup> Histopathological examination is required to make the diagnosis.

### Histological and Immunohistopathology

Although the histological type, immunohistopathology, and molecular alterations are the same among PHGIST and GIST, this information can help exclude other types of liver tumors, such as liver mesenchymal tumors, melanoma, or carcinoma. It is also valuable for evaluating recurrence. There are three histological types of PHGIST, which include spindle cell, epithelioid cell, and mixed cell. Of these, the spindle cell is the most common. Although no association has been reported between PHGIST and histologic subtype recurrence, it has been shown that epithelioid and mixed-type gastric GISTs are associated with recurrence (hazard ratio [HR], 5.73; 95% confidence interval [CI], 1.29–25.53;  $p = 0.022$ ).<sup>17</sup>

CD117 (c-kit) is expressed on germ cells, hematopoietic stem cells, and early hematopoietic progenitors, but only retained on mast cells, breast epithelium, and melanocytes after cellular differentiation. PDGFRA is found on fibroblasts and cells of mesenchymal origin. It belongs to the receptor

tyrosine kinase family, which includes c-kit.<sup>18</sup> CD34 is present on hematopoietic stem cells, hematopoietic progenitor cells, and mesenchymal stromal cells.<sup>19</sup> Although there is no known frequency correlation between mutations and histological subtype, it is thought that GISTs with PDGFRA mutations follows a more indolent course with a favorable prognostic outcome. The tumor cells of most patients are also positive for CD117 and CD34.<sup>4</sup> Cells are rarely negative for these. c-KIT and/or PDGFRA must be positive for diagnosis. However, a minor subset of GISTs lack c-KIT expression, but have PKC (protein kinase C) which is activated in the interstitial cells of Cajal and GIST. When DOG-1 (discovered on GIST1) was discovered, it was initially thought to be specific for GIST. However, it has also been found in non-GIST. Thus, only in the appropriate context can it be helpful in the diagnosis of GIST.<sup>20</sup> Because no histological features by which PHGIST can be distinguished from metastatic GIST, imaging, and other diagnostic tests to exclude extrahepatic disease are required before diagnosing PHGIST.

### Clinical management

First-line therapy for PHGIST is the surgical removal of operable tumors. Nonresectable tumors require systemic treatment (Fig. 2).

### Systemic therapy

As PHGISTs have the same histology and immunochemistry as GISTs, they are treated in the same way. The selective tyrosine kinase receptor inhibitor (TKI), imatinib mesylate, has been used as adjuvant or neoadjuvant therapy. Imatinib mesylate, a selective inhibitor of KIT and PDGFRA, has revolutionized the treatment of GIST. However, up to 14% of GISTs develop primary resistance to imatinib, defined as progression within 3 to 6 months of starting therapy<sup>20–23</sup> and 40–50% develop secondary resistance within 2 years of starting therapy.<sup>20–23</sup>

Tumor genotypes are important to determine and need to be correlated with molecular types and drug therapy to increase understanding of pathways for successful treatment and to provide more insight concerning resistance.<sup>24</sup> KIT exons 11 and 9 mutations are the most common sites associated with resistance to imatinib at 70% and 15%, respectively. Exons 13, 14, and 17 have also been associated with resistance, but not as frequently as exons 11 and 9.<sup>11,23</sup> In 2006, Wardelman *et al.*<sup>25</sup> found that resistance was associated with mutations in exon 11 and exon 9, 68.8%, and 28.6% of the time, respectively. Ten of the 32 patients developed secondary KIT mutations at exons in 13, 14, or 17 in seven, six, and five tumors, respectively. They found there was no significant difference in overall survival (OS) among patients with or without the secondary mutations. The study had a longer follow-up than with other, similar studies. However, the number of recurrences and mutations might have been underestimated as they may take a longer time to develop. The authors reassessed the response to imatinib every 3 months, which helped detect early tumor progression.

A clinical trial comparing 1 and 3-year imatinib in patients with operable GIST reported prolonged relapse-free survival (RFS) and overall survival (OS) at 5 years in the 3-year adjuvant imatinib arm.<sup>26</sup> A study strength was that most patients had biopsy-proven GIST. c-KIT and PDGFRA mutations were present in 91% of patients who underwent mutation analysis. Imatinib was reported to be well tolerated in a study among study participants. However, imatinib had to be discontinued in 12.6% of the patients in the 1 year and 25.8%

in the 3 year adjuvant imatinib arms, resulting in GIST recurrence. Study limitations were short follow-up. Longer follow-up would provide further information about the safety or efficacy of adjuvant imatinib therapy. PDGFRA mutations and c-KIT exon 11 insertion or duplication mutations were reported to be associated with better RFS, whereas c-KIT exon 9 mutations were reported to be associated with unfavorable outcomes. PDGFRA exon 18 D842V mutation was reported to be completely resistant to tyrosine kinase inhibitors.<sup>26</sup> This is a keystone study indicating the importance of implementing continuous imatinib.

A prospective multicentric randomized phase-3 study comparing interruption versus continuation of imatinib among 182 patients with advanced GIST showed statistically significant disease progression in 26/32 patients in the interrupted arm compared with 8/26 of patients in the continuous arm.<sup>27</sup> Overall survival or imatinib resistance among the arms was not significantly different between the two arms. The conclusions justified the continuous use of imatinib as long as significant toxicity does not occur.

Sunitinib is a second-line treatment used in patients with imatinib-resistant GIST. A randomized clinical trial investigating the efficacy of sunitinib among patients advanced GIST after the failure of imatinib showed a median time to tumor progression of 27.3 weeks compared with 6.4 weeks in the sunitinib arm and control arm, respectively.<sup>28</sup>

Regorafenib is the third-line treatment for patients with irresectable or metastatic GIST who are intolerant to imatinib and sunitinib.<sup>24</sup> A phase 3 double-blind, multicenter trial including 199 patients with metastatic and/or unresectable GIST who failed with imatinib or sunitinib treatment.<sup>24</sup> Patients were randomized to 160 mg/daily of regorafenib versus placebo. Median progression-free survival for regorafenib was 4.8 months and 0.9 months for the placebo arm (HR: 0.27, 95% CI: 0.19–0.39;  $p < 0.0001$ ). Grade 3 or higher side effects included hypertension, hand-foot skin reaction, and diarrhea at 23%, 20%, and 5%, respectively.

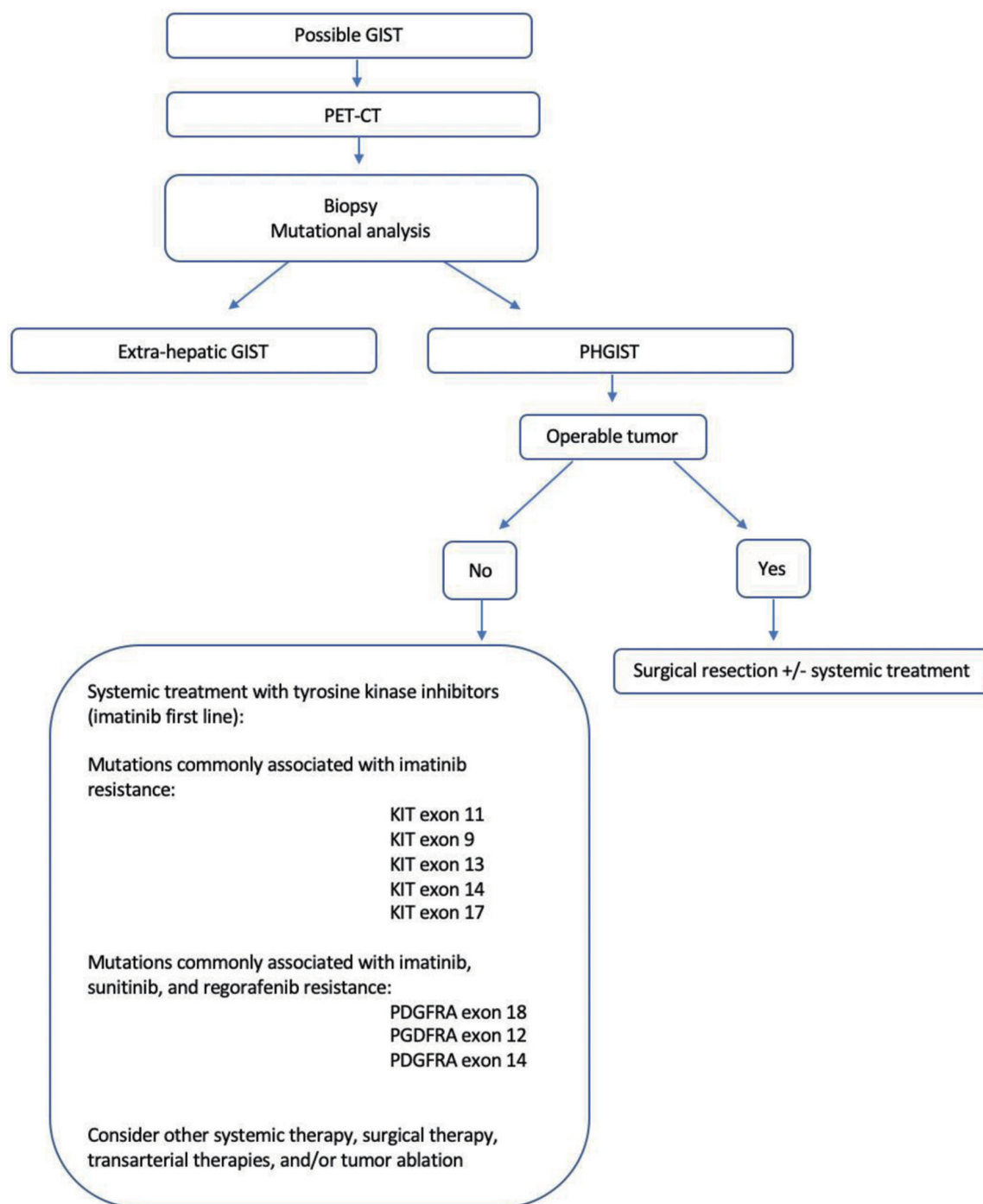
PDGFRA mutations 18, 12, and 14 have been reported to be associated with resistance to imatinib, sunitinib, and regorafenib, listed from high to low frequency, respectively.<sup>11</sup> It is unclear at this time what percentage of patients develop resistance with PHGIST compared to GIST. Other treatments can be used in combination, such as resection, transarterial therapies, and tumor ablation.

### Surgical therapy for resistant tumors

Unfortunately, several case reports have documented that patients with tumors resistant to tyrosine kinase inhibitors who underwent surgical resection alone have poor prognoses. In 2019, Xu *et al.*<sup>5</sup> reported a case of primary hepatic GIST invading the adrenal gland that was composed of epithelial cells positive for CD-117 and SDH with only one mutation at PDGFRA exon 12. Appropriate imaging supported the diagnosis of PHGIST. The patient was not treated with imatinib and sunitinib, as a previous report found that that combination was not effective for PHGIST without significant mutations of c-KIT and PDGFRA genes. The tumor was resected. However, 11 months later, the patient succumbed to PHGIST metastasis to the bone. It is unclear from the article if the authors considered third-line treatment with TKI, regorafenib, as it was not commented on in the article. Treatment after the tumor progressed to metastatic disease without liver recurrence was not discussed in the article.

Fernandes *et al.*<sup>29</sup> described a CD117-positive PHGIST that caused mass-effect symptoms and was treated with transarterial embolization (TAE) with no improvement in symp-





**Fig. 2. An algorithm for the workup to differentiate PHGIST from extrahepatic GIST.** GIST, gastrointestinal stromal tumor; KIT, tyrosine kinase; PDGFR(A), platelet-derived growth factor receptor alpha; PET-CT, positron emission tomography-computed tomography scan; PHGIST, primary hepatic gastrointestinal stromal tumors.

toms. A near-complete resection was completed because of the large size and central location of the mass with adjuvant imatinib. On follow-up 6 months later, she remained asymptomatic with no evidence of tumor development.<sup>29</sup> That was the first report of cytoreductive surgery in a patient with PHGIST. Unlike other cases in which TAE was used, the patient did not have significant shrinkage of the tumor despite its hypervascularity, and she developed side effects from the

mass effect. Further prospective studies with a larger sample size are needed to support these conclusions.

### Transarterial therapies

Another treatment includes transcatheter arterial chemoembolization (TACE), which is typically a palliative option. However, intra-arterial infusion with chemotherapy may not

be possible, such as cases with transcatheter arterial embolization (TAE). To date, there are no standard treatments after tyrosine kinase inhibitor failure, but some studies have reported success with the use of TACE and TAE in GIST with metastatic liver disease.<sup>30</sup> For example, Cao *et al.*<sup>30</sup> compared embolization and chemoembolization and found that TACE was effective and well tolerated in patients with GIST liver metastases after TKI failure either from resistance or intolerance to treatment. In their retrospective analysis of 60 patients, 22 received TACE and TKI reintroduction and 38 were controls with TKI reintroduction alone. The TACE and TKI combination was well tolerated. Post-embolization complications in most patients included mild abdominal pain, fever, and nausea. Unfortunately, there was no statistically significant difference ( $p=0.638$ ) in OS between the two groups. The median overall progression-free survival and median OS in the TACE group were longer than those in the control group at 30 vs. 13 weeks and 69 vs. 26 weeks, respectively. The study showed there may be clinical significance which was not represented statically because the low population size. Furthermore, the patients all had metastatic disease. Subgroup analysis found prolonged survival in patients without extrahepatic metastasis, result consistent with those of previous studies.<sup>31</sup> These studies used TACE as a palliative option when TKI's failed. However, additional studies are needed to determine whether there is a benefit to using it earlier as an adjuvant to TKI. Additionally, the reported findings followed only one session of TACE. The benefits of multiple TACE sessions thus remain unknown.

Two cases of TACE in patients with spindle cell PHGIST have been reported.<sup>4,14</sup> Tumor rupture is an adverse event associated with GIST regardless of location. Thus, it is important to consider whether guided tumor biopsy is necessary or whether total resection can be completed before a definitive diagnosis. Tumor size and location are decisional factors regarding biopsy versus total resection. To date, no studies have been completed regarding whether patients would have improved prognosis if TAE and TACE were given along with tyrosine kinase.

### Tumor ablation

Radiofrequency ablation (RFA) and microwave ablation are recommended in patients who are not candidates for surgery or as neoadjuvant with surgery. The combination allows for a reduction in tumor size.<sup>32</sup> After RFA treatment, it is recommended that imatinib be continued as maintenance therapy post-procedure.<sup>32</sup>

A retrospective review of 24 patients was performed by Yoon *et al.*<sup>32</sup> to evaluate the effectiveness and safety of providing intraoperative radiofrequency ablation (IORFA) along with imatinib therapy in patients with unresectable GIST with metastases to the liver. The patients had an unacceptably high risk of hepatic insufficiency alone, did not tolerate major parenchymal resection, or had tumors in locations unfavorable for surgical resection alone. Of those patients, 20 underwent hepatic resection. Patients were followed up for an average of 50.7 months. Two of the patients experienced tumor recurrence and were found to have developed resistance to imatinib, which led to changing the chemotherapy regimen. Two patients died during follow-up, one from nonrelated causes and the other from tumor progression. The GIST-specific survival rates were 100%, 94.4%, and 94.4% at 1, 3, and 5 years, respectively. IORFA allowed surgery in patients who were not initially considered to be surgical candidates because of variability in size, location, or number of tumors. The study found that RFA and surgical

resection were complementary and beneficial in cases with inoperable tumors. Imatinib before and after RFA increased therapeutic response and decreased tumor recurrence compared with other studies in which imatinib was used only before or after RFA or not at all.<sup>15,32</sup> The study was performed only on patients with PHGIST. However, due to the similarity of PHGIST and GIST, the GIST findings are probably generalizable to the PHGIST population. Other limitations include small sample size, lack of a control group, and retrospective aspect.

With only two cases reported using RFA and microwave ablation therapy in PHGIST, there is insufficient evidence to support its use or report long-term outcomes.<sup>31,33</sup> However, studies of its use in GIST have reported better outcomes and clinical progression. It is recommended in patients who are not candidates for surgery or as a neoadjuvant with surgery. Other ablative options that could be considered in these patients are cryoablation, ethanol injection, and external beam radiotherapy. There are no reports of these ablative options being used for PHGIST at this time. However, these have been reported to be used in GIST. Because of the limited number of PHGIST cases, no data efficacy or survival rates have not been published.

### Conclusion

PHGIST is a rare, complex disease that is frequently found incidentally and often overlooked, leading to missed or delayed diagnosis. Some studies reported a predilection for men and more cases have been reported in patients of Japanese and Chinese ethnicity, but cases have been reported worldwide. The ability of PHGIST to occur sporadically is concerning. Although diagnosis is one of exclusion, a systematic approach leads to an early and accurate diagnosis. Many aspects of the significance of histological type, immunohistopathology, and mutations remain unclear.

A strategic approach with surgical therapy and combination tyrosine kinase inhibitors should be considered for all patients. Surgical resection is the only curative treatment. If total resection is impossible, debulking surgery with adjuvant/neoadjuvant TKI inhibitors can be considered. Tyrosine kinase inhibitors are an alternative treatment option if complete surgical resection is not possible. Transarterial treatment, such as TACE and TAE, have had promising results. However, advanced and effective management of PHGIST requires further analysis of mutation resistance with standard treatment and long-term follow-up to provide physicians with screening guidelines before disease progression occurs.

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### Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

### Author contributions

Study concept (ECB, GYW), drafting of the manuscript (ECB,

GO), and critical revision of the manuscript for important intellectual content (ECB, GO, GYW).

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