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ABOUT COVER

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MINIREVIEWS

Prevalence, diagnosis, and treatment of primary hepatic gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GIST), which is the most common mesenchymal tumor of the digestive tract, account for 1%-3% of gastrointestinal tumors. Primary stromal tumors outside the gastrointestinal tract are collectively referred to as extra GISTs, and stromal tumors in different regions often have different prognoses. A primary hepatic GIST is a rare tumor with an unknown origin, which may be related to interstitial Cajal-like cells. Although primary hepatic GIST has certain characteristics on imaging, it lacks specific symptoms and signs; thus, the final diagnosis depends on pathological and genetic evidence. This review summarizes all cases of primary hepatic GIST described in the literature and comprehensively analyzes the detailed clinical data of all patients. In terms of treatment, local resection alone or with adjuvant therapy was the prioritized choice to obtain better disease-free survival and longer survival time. For advanced unresectable cases, imatinib mesylate was applied as the first-line chemotherapy agent. Moreover, transcatheter arterial chemoembolization,

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radiofrequency ablation, and microwave ablation were shown to improve overall survival for selected patients. Liver transplantation was a final treatment option after resistance to chemotherapy developed.

Key Words: Extra gastrointestinal stromal tumor; Treatment; Liver transplant; Review

Core Tip: A primary hepatic gastrointestinal stromal tumor(PHGIST) is a rare tumor with an unknown origin and bad prognosis, which has always been misdiagnosed. The majority of studies of PHGIST are case reports, and clinical evaluation of different treatment methods has never been established. This review, including 35 cases from different nations, summarizes the etiology, clinical characteristics, diagnosis, treatment, and prognosis of PHGIST in order to clarify the treatment options for this rare disease.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal mesenchymal tumor with an incidence of approximately 1/100000 to 1.6/100000 per year[1-3]. They are a sophisticated mesenchymal tumor, mainly including immature spindle-shaped and/or epithelial-like cell proliferations. Studies have shown that tumorigenesis originates from the interstitial cell of Cajal (ICC) in the gastrointestinal tract, which is the cell responsible for triggering gastrointestinal mobility[4]. The diagnosis of GIST is based on the pathology of the lesion, including cell morphology and immunohistochemistry. According to previous research, CD117 (c-KIT) is expressed in approximately 94%-98% of GIST cases, while CD34 is expressed in 70% of cases[5,6]. GIST occurs in the digestive tract, including the stomach (60%-70%), the small intestine (20%-25%), the colon and rectum (5%), and the esophagus (< 5%)[7].

An extra GIST (EGIST) refers to a type of tumor similar to GIST in tissue morphology and immunophenotype but that originates in the abdominal cavity or retroperitoneum and does not involve the intestinal wall or visceral serosa[8]. Presently, there is no unified understanding of the origin of EGIST due to its low incidence. According to the study by Du *et al*[9], the incidence of EGIST is < 10% of all GISTs with a definite source. The malignant risk of the tumor, defined as its ability to invade and metastasize, is varied. GISTs are classified into four levels according to their size, mitotic image, and location of the lesion using the National Institutes of Health (NIH) classification guideline, which corresponds to different prognoses and preferred treatment methods. According to previous reports, the risk classification and prognosis of EGISTs are significantly worse than those of gastrointestinal tumors[10,11].

Both GIST and EGIST commonly metastasize to the liver[12-14], but the liver is a rare primary metastatic site of GIST. The majority of studies of primary hepatic GIST (PHGIST) are case reports, and clinical evaluation of different treatment methods has never been established. However, an overall impression of the clinical features, imaging, pathology, and treatment prognosis of PHGIST can be obtained from the limited literature. This review summarizes the etiology, clinical characteristics, diagnosis, and treatment of PHGIST, including cases from the earliest reports found to December 2019. Moreover, this review attempts to clarify the survival and treatment options for this rare disease.

SEARCH FOR CASE REPORTS OF PHGIST PATIENTS

Online databases, including PubMed and China National Knowledge Internet, were used to find relevant studies and further analyze the characteristics of PHGIST without restrictions on publication dates until December 1, 2019. The search terms used were as follows: "extra-gastrointestinal stromal tumors," "gastrointestinal stromal tumor and liver," "primary hepatic gastrointestinal stromal tumors," and "stromal tumors of the liver." The references for initial studies found were scanned carefully to identify more studies. Eligible documents were selected according to the abstract, and the entire report was subsequently reviewed cautiously. We collected and recorded all reports containing detailed patient information including medical history, laboratory and imaging data, pathological information, treatment records, and prognostic methods (Table 1).

ETIOLOGY OF PHGIST

ICCs are interstitial cells found in the gastrointestinal tract that function as pacemakers for gastrointestinal peristalsis[4]. Current research suggests that GISTs originate from this cell[15]. Moreover, ICC-like cells with a similar structure and function to ICC were observed in organs outside the digestive tract as well as in the vasculature, including the portal vein and mesenteric artery space, using immunohistochemistry in human and animal specimens[16,17]. Rusu *et al*[18] and Ilie *et al*[19] demonstrated that ICC-like cells were also present in the human embryonic liver as a single precursor/progenitor cell. Therefore, it is reasonable to speculate that PHGISTs originate from this typical ICC-like precursor cell. Some authors also believe that PHGISTs originate from undifferentiated pluripotent mesenchymal stem cells located outside the gastrointestinal tract that then differentiate into ICC[10]. The occurrence of PHGIST on all liver lobes indicates that the distribution of ICC cells in the liver is widespread, and the presence of ICC-like cells in liver tissue may contribute to the development of PHGIST.

The mechanism underlying how ICC develops into a tumor remains largely unknown. Several studies have shown that the function-acquired mutation stem cell factor receptor (*KIT*) of the receptor tyrosine kinase gene in ICC plays a crucial role in the occurrence of most GIST cases[20]. In previous studies, 65%-80% of GISTs had mutations in the *KIT* gene, and approximately 10% of KIT-negative GISTs had activation mutations in the platelet-derived growth factor receptor alpha (*PDGFRA*) gene[21,22]. In our review, nine patients with gene analysis were included, and the mutation rate was 66% (6/9; n = 4 for *KIT* gene, n = 2 for *PDGFRA* gene). *KIT* and *PDGFRA* mutations may also promote the occurrence and development of PHGIST *via* activation and autophosphorylation of downstream signaling pathways.

CLINICAL FEATURES AND LABORATORY TESTS FOR PHGIST

PHGIST patients may have no obvious symptoms with a liver mass accidentally found during routine physical examination or imaging with subsequent confirmatory diagnostic testing. Symptomatic patients show symptoms similar to chronic liver disease, and abdominal pain and a palpable abdominal mass are the most common presentations. Other presenting gastrointestinal symptoms include abdominal discomfort, indigestion, and distension. It is worth noting that two patients presented with significant, acute weight loss in the late stage[23,24]. Some patients may have difficulty breathing because of a large tumor resulting in mechanical obstruction[25,26]. In the later stage of tumor growth, tumor rupture and bleeding can occur, and patients present to the hospital due to sudden onset abdominal pain[27]. Although the incidence is rare, the possibility of GIST should be considered clinically for large space-occupying lesions of the liver. PHGIST is currently not associated with any specific tumor marker, except for a few cases that presented with slightly elevated but within normal range alpha-fetoprotein, CA19-9, and CA125 levels[11].

IMAGING AND PATHOLOGICAL DIAGNOSIS

Given that there are no specific radiological features for PHGIST, it is challenging to

Table 1 Case reports of primary hepatic gastrointestinal stromal tumors

Ref.	Year	Nation	Age/sex	Symptom	Location/*n*	Size in cm	Tumor presentation	Rupture	Treatment	Cell morphology	Mitotic, /50 HPFs	IH (+)	*Ki67*, %	Test for gene mutation	Risk	Recurrence	OS
[25]	2003	United States	79/F	Short of breath	R/1	15	Solid + cyst	No	HR	S	20	CD117, CD34	15	No	High	16/Met	20/A
[42]	2006	Italy	37/M	No symptom	R/1	18	Solid + cyst	No	HR	S	20	CD117	NA	No	High	14/Met	39/A
[51]	2006	China	62/M	AP	R + L/2	14.5	Solid + cyst	No	HR	S	NA	CD117, CD34	NA	No	High	NA	NA
[52]	2006	China	45/M	AP	R/> 3	20	Cyst	No	Drainage	S	35	CD117, CD34	50	No	High	3/DFS	NA
[26]	2007	China	67/M	Short of breath, distention	L/1	44	Solid + cyst	No	HR	NA	> 3	CD117, CD34	NA	No	High	4/DFS	4/A
[53]	2008	China	48/F	No symptom	L/1	4.3	Solid + cyst	No	Chemo	NA	NA	CD117	NA	No	NA	NA	NA
[44]	2009	China	17/M	No symptom	R/1	5.1	Solid	No	RFA	S	0	CD117, CD34	NA	No	High	3/DFS	3/A
[54]	2009	Japan	30/M	Abdominal fullness	R + L/1	20	Solid + cyst	No	HR	S + E	75	CD117, CD34	NA	Yes, negative	High	24/Rec + Met	108/A
[33]	2010	Japan	70/M	Appetite reduced	L/1	20	Solid	No	HR	E	1	CD34	NA	Yes, *PDGFRA 12*	High	NA	NA
[55]	2010	China	40/F	No symptom	L/1	18	Cyst	No	HR	S	> 5	CD117	> 5	No	High	12/DFS	12/A
[56]	2012	China	53/M	Abdominal discomfort	R/1	20	Solid + cyst	No	No treatment	NA	NA	CD117, CD34, DOG-1	NA	No	High	NA	NA
[57]	2012	China	65/F	No symptom	R/1	NA	Solid + cyst	No	Chemo	S	NA	CD117, CD34	NA	No	High	NA	NA
[58]	2013	China	66/F	Distention	L/1	8.6	Solid + cyst	No	HR	S	35	CD117	NA	No	High	12/Rec + Met	13/D
[59]	2013	China	71/M	No symptom	R / 1	10	Solid	No	HR	S	NA	CD117, CD34, DOG-1	NA	No	High	NA	NA
[60]	2014	India	55/F	AP, Appetite reduced	R + L/3	18	Solid	No	HR	S	10	CD117	NA	No	High	7/DFS	7/A
[28]	2014	Korea	71/M	Nausea, indigestion	L/1	7	Solid + cyst	No	HR	S	30-32	CD117, DOG-1	NA	No	High	19/DFS	19/A

[31]	2014	China	56/M	No symptom	R + L/1	10	Cyst	No	HR	S	< 5	CD117	NA	No	High	12/DFS	12/A
[24]	2014	India	41/F	AP, weight loss	R/2	15	Solid + cyst	No	HR	S	NA	CD117	NA	No	High	5/DFS	5/A
[37]	2015	China	60/F	No symptom	R + C/1	19	Solid + cyst	No	HR + AT	S	10	CD117, DOG-1	NA	Yes, *KIT* exon 11	High	12/DFS	12/A
[61]	2015	China	65/M	AP, appetite reduced	L/1	12	Solid + cyst	No	Chemo	S	25	CD117	NA	Yes, negative	High	13/Met	13/D
[36]	2015	China	67/F	No symptom	R/1	7.4	Solid + cyst	No	HR	S + E	8	CD117, CD34	NA	Yes, *KIT* exon 11	High	14/Rec	50/A
[62]	2015	China	48/F	AP	L/1	17.6	Solid + cyst	No	HR	NA	NA	CD117, CD34, DOG-1	NA	No	High	NA	NA
[45]	2016	China	56/F	No symptom	L/1	2.4	Solid	No	MWA	S	1-2	CD117	60	No	High	17/Met	17/A
[63]	2016	Chile	61/M	AP	L/1	15	Solid + cyst	No	HR	NA	NA	CD117, CD34	NA	No	High	NA	NA
[64]	2016	China	61/M	No symptom	C/1	7.3	Solid + cyst	No	HR	S	NA	CD117, CD34, DOG-1	2	No	High	11/DFS	11/A
[32]	2016	Japan	70/F	No symptom	L/1	6.8	Solid + cyst	No	HR	S	35-40	CD117, CD34	NA	No	High	10/DFS	10/A
[65]	2016	China	63/M	No symptom	R/1	13	Solid + cyst	No	HR	S	> 5	CD117, CD34	NA	No	High	60/DFS	60/A
[11]	2019	China	64/F	AP	R/1	15	Solid + cyst	No	HR	S	> 5	CD117	NA	Yes, *PDGFRA 12*	High	5/DFS	5/A
[27]	2017	China	50/F	Onset AP	R/1	15	Solid + cyst	Yes	HR	S	70	CD117, CD34	NA	No	High	6/Met	6/A
[66]	2017	China	57/F	No symptom	L/1	4	Solid + cyst	No	HR	S	NA	CD117, DOG-1	10	No	NA	6/DFS	6/A
[43]	2017	China	45/F	No symptom	R + L/> 3	11.5	Solid	No	TACE + HR	S	5	CD117, CD34, DOG-1	3	Yes, negative	High	1/Met	18/A
[30]	2017	Spanish	41/M	Abdominal discomfort	R + L/1	20	Solid	No	HR	S	5	CD117, DOG-1	10	Yes, *KIT* exon 11	High	18/DFS	18/A
[23]	2018	France	56/M	AP	R/1	10	Solid	No	TACE + HR + T + Chemo	S	8	CD117, CD34	NA	No	High	12/Rec	264/D
		France	59/F	AP, weight loss	R + L/1	23	Solid + cyst	No	Chemo	S + E	42	CD117, DOG-1	30	Yes, *KIT* exon 9	High	18/DFS	18/A

[67]	2018	China	74/M	Abdominal discomfort	R/1	5.5	Solid + cyst	No	HR	S	< 5	CD117, DOG-1	15	No	High	NA	NA

AP: Abdominal pain; AT: Autotransplantation; C: Caudate lobe of liver; Chemo: Chemotherapy; DFS: Disease-free survival; E: Epithelioid; F: Female; HPF: High-power field; HR: Hepatic resection; IH: Immunohistochemistry; L: Left lobe of liver; M: Male (sex), and median lobe of liver (location); Met: Metastasis; MWA: Microwave ablation; NA: Not available; OS: Overall survival; R: Right lobe of liver; Rec: Recurrence; RFA: Radiofrequency ablation; S: Spindle; TACE: Transcatheter arterial chemoembolization; T: Transplantation.

distinguish PHGIST from other hepatic tumors preoperatively. Thus, these types of tumors are often misdiagnosed. From a morphological point of view, most PHGISTs appear as single round cyst-like solid masses that are occasionally lobulated with bright or fuzzy borders and thick pseudo capsules in some parts with central necrosis and cysts. Tumors may be accompanied by intratumor bleeding, and calcification is rare. It is worth mentioning that magnetic resonance imaging is useful in showing the complex components of tumor tissues[28]. Specifically, diffusion-weighted imaging for solid components shows a significantly high signal, which may be related to malignant tumors[29].

Two types of enhancement imaging patterns for most contrasted scans were seen. First, during the arterial, portal, and delay phases, there was continuous uneven enhancement. If the tumor was a solid mass, it was often difficult to distinguish from hepatic hemangioma[30]. Second, on the fast-forward and fast-reverse phases, the arterial phase was significantly strengthened to a level higher than the normal liver parenchyma. Identification was challenging when equal or low density signals were similar to those for hepatocellular carcinoma, especially when the lesion had a false capsule[11]. In one case, an entirely cystic tumor was seen, which was difficult to distinguish from a hepatic cyst during the early stage. Its size increased during the follow-up course, and PHGIST was finally confirmed[31]. Follow-up imaging studies should be performed, and a diagnosis of PHGIST should be suspected if there is rapid tumor enlargement.

In GIST, positron emission tomography-computed tomography (PET-CT) is considered to be the most sensitive method for diagnosis as well as for evaluating the efficacy of molecularly targeted drugs. Because PET-CT has essential value in diagnosis and staging, prediction of malignant potential, treatment decision, efficacy assessment, and follow-up monitoring, it has been clinically recognized and included in the 2010 National Comprehensive Cancer Network Guide Guidelines Medium[6]. In the literature, PET-CT was used to exclude liver GIST from extrahepatic lesions with a maximum standardized uptake value of 6.30-6.85[28,32]. Importantly, even if patients have a characteristic image without a history of hepatitis and alpha-fetoprotein levels are not elevated, the possibility of PHGIST should be considered in the differential diagnosis. However, the final diagnosis should still be based on pathology and immunohistochemistry.

EGISTs have the same morphology, immunohistochemistry, and molecular characteristics as conventional GISTs, including metastatic GISTs. The

histopathological diagnostic criteria for GISTs have been firmly established. Histologically, there are three main PHGIST types. The spindle cell type predominates, while epithelioid cell and mixed cell types account for only a small portion of cases (11.4%, 4/35). The tumor cells of most patients who underwent immunohistochemistry expressed CD117 and CD34, which showed a positive envelope and/or diffuse cytoplasm. Only one case of GIST was found not to express CD117, but it was CD34 positive[33]. The diagnosis of GIST cannot be ruled out in a patient with a tumor morphologically consistent with GIST but without CD117 expression. In this case, further detection of mutations in the *c-KIT* and *PDGFRA-a* genes is required for diagnosis. Moreover, GISTs can also express DOG1, especially in cases with a *PDGFR-a* gene mutation without a *c-KIT* mutation with an overall sensitivity similar to that of CD117[34]. The combination of DOG1 and CD117 expression for the diagnosis of GIST has functional complementarity[35].

We believe that a precise diagnosis requires immunohistochemistry and molecular examination, which may exclude other rare types of hepatic mesenchymal epithelioid tumors, such as epithelioid vascular leiomyomata, leiomyosarcoma, and malignant melanin tumors. It should be emphasized that the liver is the most likely place for GIST metastasis and that primary GIST of the liver is rare. Therefore, to ensure an accurate diagnosis, it is necessary to exclude tumors in other common locations of the gastrointestinal tract by using methods such as barium radiography, digestive endoscopy, and PET-CT. In addition, CT or ultrasound-guided fine-needle aspiration biopsy is commonly used to diagnose unresectable hepatic tumors[23,36]. Puncture biopsy can also be used to definitively diagnose patients with inoperable PHGIST.

OVERALL CONDITION OF THE CASE REPORTS

There were 34 reports of PHGIST in the literature, with a total of 35 cases as follows: twenty-three in China, one in South Korea, two in France, two in India, three in Japan, and four in other countries (Table 1). Patients ranged in age from 17-79 years with an average age of 56 years. Seventeen cases were male, seventeen cases were female, and one case had no reported gender. Of all cases, 26.6% (15/35) were asymptomatic and found on routine physical examination. The presenting symptom was abdominal pain of varying intensity in 11 patients. One case presented with acute rupture due to tumor rupture, and the other presenting manifestations included loss of appetite (n = 2), indigestion (n = 1), abdominal discomfort (n = 2), weight loss (n = 2), and shortness of breath (n = 2). Tumors were located in all lobes of the liver with the majority being in the right lobe (n = 22). Most patients presented with a single hepatic mass (n = 30); however, two patients had more than two masses. The tumors ranged in diameter from 2.3 cm to 44.0 cm (median, 15.0 cm; mean, 13.8 cm). On imaging, there were three, eight, and twenty-four cases of cystic masses, solid masses, and mixed masses, respectively.

Of the thirty-five patients, twenty-five underwent local hepatectomy alone or in combination with adjuvant therapy, two underwent transcatheter arterial chemoembolization (TACE), and two underwent liver transplantation. Three patients received different interventions for various reasons: One patient (tumor size 5.1 cm) underwent radiofrequency ablation, one patient (tumor size 2.4 cm) was treated with microwave ablation, and one patient with large cystic masses (largest tumor > 20 cm) underwent repeated cystic drainage. The remaining five cases were not treated surgically, including one patient who was discharged without any treatment. Follow-up data were obtained from 24 patients, and recurrence usually occurred within 1 year of the operation. The metastatic sites included the liver, lymph nodes, bones, and brain. Most patients were categorized as high risk according to the risk stratification criteria of the 2008 version of the NIH guidelines, and 16 patients received adjuvant therapy or chemotherapy alone. Nineteen of twenty-five patients (76.0%) had a mitotic index ≥ 5/50 high-power fields.

Ki-67 expression was detected in ten patients, and eight patients had a ratio more than 5%. Among thirty liver GIST specimens, spindle cell morphology was observed in twenty-five (83.3%), epithelioid cell morphology was observed in one (3.3%), and mixed cell morphology was observed in four (13.3%). Of the 35 (97.1%) specimens, 34 were positive for CD117, and 18 (51.4%) were positive for CD3. Five of six cases (83.3%) were positive for DOG-1. Genomic mutations were examined in four specimens. *KIT* mutations in exon 11 were found in three of nine specimens, *KIT* mutations in exon 9 were found in one specimen, *PDGFE 12* mutations were found in two specimens, and the remaining three specimens had no apparent genetic

mutations. The 2008 version of NIH risk classified thirty-three patients as high risk (94%), and the other two patients could not be classified because of incomplete data. Seventeen studies reported prognostic results. During follow-up, five patients were diagnosed with recurrent or metastatic tumors. Metastases were found in the following organs: hilar and pulmonary lymph nodes (n = 1), stomach (n = 1), lungs (n = 1), brain (n = 1), and bone (n = 1). Two patients who did not undergo surgery died of primary liver EGIST at 13 mo.

PHGIST TREATMENT

As there are few cases of PHGIST, the main treatment methods follow the treatment protocol of GIST, which reflects the concept of comprehensive therapy as a whole. Based on a review of all cases, we believe that lesion resection with or without combined chemotherapy is the best choice. Of the 30 patients with PHGIST who received local hepatectomy alone or in combination with chemotherapy, 23 (76.7%) patients had a survival > 6 mo. For locally advanced tumors, after an evaluation is performed, obtaining R0 resection should be attempted followed by adjuvant treatment. In one case, a liver mass was located in the right posterior lobe of the liver, which spread to the right adrenal gland[11]. Because conventional methods could not be used for resection, external hepatectomy and autotransplantation were performed[37]. Interestingly, the majority of reported cases of PHGIST were detected at a resectable stage with < 15% of patients not being treated with surgery.

According to the recommendations of the NIH, almost all PHGISTs are high risk and thus require adjuvant treatment. Among chemotherapeutic agents, imatinib is recommended as a first-line treatment[38,39], although less common drugs such as sunitinib and regorafenib are sometimes used[40,41]. GIST is caused by *c-KIT* or *PDGFR* mutations in precursor cells, leading to the continuous activation of tyrosine kinase and uncontrolled cell proliferation and differentiation. Therefore, the use of imatinib, a tyrosine kinase inhibitor, has completely changed the concept of surgical treatment and comprehensive treatment of GIST[38]. For PHGIST, almost half of the patients studied received imatinib as a basic or adjuvant treatment with satisfactory results. Although no patient received imatinib as a preoperative adjuvant treatment, we believe that after the evaluation of certain advanced tumors, it can be used as neoadjuvant therapy to minimize the lesion and obtain possible R0 resection.

Imatinib is also the first-line therapy recommended for patients with unresectable tumors or who have obvious contraindications to surgery. A needle biopsy is required to confirm the diagnosis for nonsurgical treatment; however, it is necessary to ensure that the biopsy is performed well. It is worth noting that in patients treated with imatinib, even if the lesion does not shrink significantly during follow-up, this may indicate stable cancer with a prolonged survival time. Joyon *et al*[23] reported a patient who had only minimal response at 6 mo follow-up (< 10% reduction in diameter), but who survived 18 mo following diagnosis. For patients who can undergo resection after relapse, the tumor should be resected, and imatinib should be added or continued. In GIST cases, the 2 years of progression-free survival for patients treated with imatinib was 77%, which may be similar for PHGIST[36,42,43]. Conventional chemotherapeutics such as doxorubicin combined with cisplatin were seldom used in PHGIST cases; however, they may contribute to the maintenance of tumor stability. In one report[36], systemic chemotherapy consisting of 50 mg/m^2 doxorubicin and 50 mg/m^2 cisplatin every 3 wk resulted in improved symptoms with reductions in dull upper abdominal pain and tumor size on palpation after the first treatment cycle.

PHGIST may be asymptomatic early, but the tumors grow quickly, and rupture and bleeding may occur. Indeed, several cases of intratumor bleeding have been reported. Transarterial embolization can be performed to stanch bleeding. Other treatment strategies are used in specific clinical situations. In two patients with small tumors, local treatment was attempted with radiofrequency[44] and microwave[45] ablation resulting in a satisfying prognosis. TACE is a palliative treatment for patients with unresectable primary hepatic angiosarcoma. Liao *et al*[43] reported a case who accepted TACE to slow tumor progression and reduce lesions, ultimately achieving R0 resection of the tumor.

Resistance to chemotherapy treatment may eventually occur with the prolongation of imatinib treatment time. For GIST, it has been reported that 15% of patients are primarily resistant to the drug[46], In general, 88% of patients suffer from recurrence about 2 years after imatinib treatment due to the secondary resistance mutations in additional *KIT* exons[47,48]. Given the poor results of palliative treatment including

chemotherapy, ablation, and TACE in patients with tyrosine kinase inhibitor drug resistance, liver transplantation may be the only treatment that may improve prognosis and prolong the overall survival time[49]. In a case reported by Joyon *et al*[23], a patient received a first course of lipiodol chemoembolization, but a second intrahepatic lesion was discovered in the left lobe 3 mo later. After evaluating the transplantation indications, liver transplantation was proposed. The patient eventually died 22 years after the initial diagnosis, 21 years after liver transplantation, and 9 years after tumor recurrence. According to the study by Frilling *et al*[50], adjuvant treatment with imatinib initially given before transplantation for a period > 2 years may yield better results. Mao *et al*[37] performed extracorporeal hepatic resection and autotransplantation for PHGIST. The patient then received imatinib adjuvant therapy and had no evidence of recurrence on CT or ultrasound after 12 mo.

LIMITATIONS OF THE ANALYSIS

Our study is a retrospective analysis based on previous literature, and it inevitably has some limitations. First, the sample size was relatively small. Only Chinese and English language literature was searched, which may have led to uneven regional sampling. Second, this review included case reports from East and South Asia, North and South America, and western and southern Europe; therefore, the demographic heterogeneity across different studies is inevitable. Third, combined case report analyses are somewhat limited and inaccurate due to the difference in the quality of care between hospitals and institutions. We tried to minimize the analysis of data from case reports and preferred to focus on the essential characteristics of the patients in these reports.

CONCLUSION

PHGISTs are sporadic. It remains challenging to accurately determine the liver as the primary site of GISTs to obtain an accurate diagnosis. The first-line treatment of PHGIST is surgical intervention. Additionally, imatinib can be used as adjuvant therapy for locally advanced tumors and as the first-line treatment for unresectable tumors, recurrence, and metastases. Overall, existing studies have shown that PHGISTs are high-risk tumors compared with common GISTs, meaning that the prognosis of PHGIST is worse than that of gastric and small intestine GIST. Therefore, involvement of a multidisciplinary team is needed for the diagnosis and treatment of patients with PHGIST.

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