Clinicopathological Features and Clinical Outcomes of Primary Hepatic Gastrointestinal Stromal Tumors: Evaluation of a Pooled Case Series

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Abstract

Background: Due to the extremely rare incidence, data of clinicopathological features and prognosis of primary hepatic gastrointestinal stromal tumors (GISTs) is limited.

Methods: 36 cases of hepatic GISTs were from the literature, PUBMED, EMBASE, China National Knowledge Infrastructure and WANFANG DATA, and 1 case came from our center. Clinicopathological features and outcomes were analyzed between 37 hepatic GISTs and 254 gastric GISTs from our center.

Results: A majority of hepatic GISTs exceeded 5 cm (83.7%), displayed mixed density (69.4%) and spindle morphology (74.2%) and were classified as high risk (91.4%). Larger tumors of hepatic GISTs were likely to display mixed lesion and tumors with mixed lesion were prone to be classified as high risk. In comparisons to gastric GISTs, hepatic GISTs differed from gastric GISTs in tumor size, main symptoms, histologic type, mitotic index, CD34 expression, NIH risk classification. In patients with hepatic GISTs, 5-year DFS and DSS rates were 19.4% and 53.7%, which were worse than that of gastric GISTs ($P < 0.001$), especially for those with tumor size exceeding 5 cm or mitotic indices exceeding 5/50 HPF ($P < 0.001$). Multivariable analysis showed location and NIH risk classification were independent prognostic factors for DFS in patients with GISTs, and size and location were significantly associated with DSS.

Conclusions: Hepatic GISTs distinguished from gastric GISTs in respect to clinicopathological features and outcomes. Mitotic index exceeding 5/50 HPF or tumor size exceeding 5 cm may be important factor to distinguish hepatic GISTs from gastric GISTs in DFS and DSS.

Background

Gastrointestinal stromal tumor (GIST) with some malignant potential is the most common gastrointestinal mesenchymal tumor and considered to originate from naive interstitial cells that differentiate into Cajal cells(ICC).[1–3] Frequent mutations in genes for *c-KIT* and platelet-derived growth factor receptor alpha (*PDGFRA*) may promote GISTs by activating or auto-phosphorylating their downstream signaling pathways.[4–5] About 70% of gastrointestinal stromal tumors show spindle-cell morphology, followed by epithelioid (20%) and mixed type (10%).[6] Immunohistochemical detection of CD117, CD34, DOG-1 plays an important role in the diagnosis of GIST.[7–8] Although GISTs account for only 1–2% of gastrointestinal malignancies, they can occur anywhere in the gastrointestinal tract,[9] which most were frequently located in the stomach(45%-65%), followed by the small intestine(15–25%), colon and rectum (5–10% in), and the esophagus(5–10%).[5] However, GISTs also occur outside of the gastrointestinal tract (pancreas, liver, gallbladder, omentum, mesentery, retroperitoneum, vagina, prostate, etc.) as primary tumor, which are identified as extra-gastrointestinal stromal tumors (EGISTs).[10–15] Studies of primary hepatic GISTs are really rare, most of which are case reports with limited data. In this study, we evaluated clinicopathological features and prognosis of primary hepatic GISTs in order to optimize the diagnosis and treatment.

Methods

Most cases of primary hepatic GIST were from the literature, and only one case came from our center. Literature search of PUBMED, EMBASE, Knowledge Infrastructure (CKNI) and WANFANG DATA was performed for all article published from December 2006 to Apr 2019, using the following Medical Subject Heading (MeSH) terms or key words: liver, gastrointestinal stromal tumor, hepatic GIST, gastrointestinal stromal tumor of the liver, E-GIST and related articles respectively. The key words were used in all possible combinations to retrieve the maximal number of articles. To collect the primary hepatic GISTs cases, the inclusion criteria of primary hepatic GISTs can be considered at following conditions: (1) Histopathological diagnosis of GIST on well-established international criteria, (2) It described gastroscopy, colonoscopy, ultrasonic endoscope or PET-CT examination or laparoscopic explore revealed no other primary GISTs in gastrointestinal tract exceptt for the mass, (3) Absence of any past medical history of GISTs in gastrointestinal tract. Exclusion criteria included: experimental studies in animal models, abstracts and editorials. Finally, a total of 37 patients with primary hepatic GISTs were included. The study evaluated a pooled series cases of hepatic GISTs regarding clinicopathological features, treatment strategies and prognosis and compared it with 254 gastric GISTs from our center. Gastric GISTs were diagnosed in our center from GIST registry between 2013 and 2019 with strictly defined criteria. This study was approved by the Ethics Committee of Liao Ning Cancer Hospital. Written informed consents were obtained from the patients in our center.

Case introduction

A 47-year-old female presented with abdominal discomfort for one month and underwent ultrasound examination which revealed a solid and mixed cystic tumor in the liver in our center. The computed tomography scan showed a heterogenous hypodense mass with a maximum diameter of 5.2 cm in the right posterior lobe of the live in Fig. 4. CT images showed peripheral enhancement in the arterial phase and progressive concentric enhancement in the portal venous phase. Magnetic resonance imaging revealed the lesion with hypointensity relative to live tissue on T1-weighted phase images and hyperintensity on T2-weighted phase images. Gastroscopy, colonoscopy and ultrasonic endoscope examination revealed no other malignancies except for the mass. The patient received a partial hepatic resection and the tumor was intactly removed. The tumor was consisted of spindle cell morphology and the mitotic index was 26/50 HPF in most proliferative areas. The immunohistochemical detection demonstrated the diagnosis of primary hepatic GISTs with the positive expression of Dog-1 and CD117 and the *c-KIT* mutation was observed in gene mutation examination. Since the tumor was divided into high risk category, according to the modified NIH risk classification, the patient received adjuvant imatinib therapy and finally died for recurrence and metastasis 4 months after operation.

Clinicopathological features were analyzed, including age, sex, symptoms (bleeding, abdominal lesion, abdominal discomfort, bloating, nausea or loss of appetite, and shortness of breath), location, size, tumor density (solid, cystic or mixed, according to imaging characteristics or pathological findings), histologic

types, mitotic index, Ki-67 expression, immunohistochemistry (IHC) detection, lymph node metastasis, gene mutation status, surgical intervention, adjuvant therapy, and modified National Institutes of Health (NIH) classification (very low risk, low risk, intermediate risk or high risk).

To analyze primary hepatic GISTs prognosis and make comparison of outcome between gastric and hepatic GISTs, we included cases for which (1) patients were diagnosed with primary GIST of the liver or stomach, without GISTs of other organs, (2) didn't suffer from other malignant tumors, (3) had no distant metastasis, (4) underwent R0 resections (6) the tumor was integrally removed (7) with follow-up data (8) didn't received preoperative adjuvant imatinib therapy.

Statistical analysis

All continuous values are presented as mean ± standard deviation. Statistical analysis was conducted using the Chi-square test or Fisher's test for categorical variables. The multivariable Cox proportional hazard model and univariate analysis were used to analyze prognostic risk factors in patients with GISTs. The Kaplan–Meier method was used to calculate survival curves for disease-free survival (DFS) and disease-specific survival (DSS); differences between the curves were assessed using the log-rank test. Data was proceeded by SPSS 23.0 software. The *P* value was considered to be statistically significant at the 5% level.

Results

The clinicopathological features of primary hepatic GISTs were summarized in Table 1. With 37 cases collected in the study, 21 cases were men (56.8%), 16 cases were women (43.2%), ranging in age from 17 years old to 79 years old (mean, 55y; median, 56 y). Their most common symptoms were abdominal pain and discomfort (28.0%), followed by bloating (20.0%), abdominal lesion (16.0%), and bleeding (4.0%). Hepatic GISTs were located in the right lobe (43.2%), followed by left lobe (37.8%), and caudate lobe (5.4%). 25 (69.4%) tumors displayed mixed lesion, 7 tumors (19.4%) showed solid lesion, and 4 (11.2%) tumors showed cystic lesion. Median tumor size was 11 cm (range: 2–44 cm; mean: 13 cm). 23 samples (74.2%) showed spindle-cell morphology, 7 cases (22.6%) showed mixed morphology, and only 1case (3.2%) displayed epithelioid morphology. Mitotic index exceeded 10/50 HPF (51.9%) in 14 samples and were less than 5/50 HPF in 9 out of 27 patients (33.3%). Ki-67 expression exceeded 5% in 7 out of the 14 cases. Positive expression of CD117 in 33 out of 34 patients, positive expression of CD34 in 20 out of 30 patients, positive expression of Dog-1 in 11out of 13 patients were discovered. Lymph node metastases occurred in 3 out of 36 patients (8.3%). With 6 samples receiving gene mutation examination, 3 specimens (50.0%) carried *c-KIT* mutation in exon 11, 1 case (16.7%) carried a *PDGFEA* mutation, and 2 cases (33.3%) failed to observe a *c-KIT* mutation or *PDGFEA* mutation status. 25 patients (71.4%) received complete resections, 1 patient (2.9%) had an incomplete resection, 2 patients (5.7%) underwent radiofrequency ablation, and 7 cases (44%) had no surgical interventions. 11patients did not receive imatinib or sunitinib therapy; and 32 patients (91.4%) were high risk according to the NIH risk classification.

Table 1
Clinicopathological features of hepatic GISTs

Clinicopathologic features	Number	Percentage(%)
Age(∑=37)(y)		
<55	16	43.2
≥ 55	21	56.8
Gender(∑=37)		
Male	21	56.8
Female	16	43.2
The main symptoms(∑=25)		
Bleeding or anemia	1	4.0
Abdominal mass	4	16.0
Abdominal discomfort	7	28.0
Bloating	5	20.0
Nausea or loss of appetite	3	12.0
Shortness of breath	3	12.0
tiredness	2	8.0
Location(∑=37)		
Left lobe	14	37.8
Right lobe	16	43.2
Caudate lobe	2	5.4
Both lobe	5	13.5
Density of tumor(∑=36)		
Solid	7	19.4
Cystic	4	11.2
Mixed	25	69.4
Size (∑=37)(cm)		
0–2	1	2.7

GISTs, gastrointestinal stromal tumors; density of tumor is determined by the imaging characteristics or pathological findings; KIT, c-KIT proto-oncogene protein; PDGFRA, platelet-derived growth factor receptor alpha; NIH, National Institutes of Health.

Clinicopathologic features	Number	Percentage(%)
2.1-5	5	13.5
5.1–10	13	35.1
≥ 10	18	48.6
Histologic types(∑=31)		
Spindle	23	74.2
Epithelioid	1	3.2
Mixed	7	22.6
Mitotic index (∑=27)		
≤ 5	9	33.3
6.0–10	4	14.8
> 10	14	51.9
Ki-67 expression(∑=14)		
<5%	7	50.0
≥ 5%	7	50.0
Immunohistochemistry		
CD117(∑=34)	33	97.1
CD34(∑=30)	20	66.7
Dog-1(∑=13)	11	84.6
Vimentin(∑=20)	19	95.0
S-100(∑=29)	0	0.0
SMA(∑=27)	7	25.9
Lymph nodes metastasis(∑=37)		
Yes	2	5.4
No	35	94.6
Genetic mutation types(∑=6)		
KIT	3	50.0

GISTs, gastrointestinal stromal tumors; density of tumor is determined by the imaging characteristics or pathological findings; KIT, c-KIT proto-oncogene protein; PDGFRA, platelet-derived growth factor receptor alpha; NIH, National Institutes of Health.

Clinicopathologic features	Number	Percentage(%)
PDGFRA	1	16.7
Wild type	2	33.3
Surgical intervention($\sum$=35)		
Complete resection	25	71.4
Incomplete resection	1	2.9
Radiofrequency ablation	2	5.7
No surgery	6	20.0
Adjuvant therapy ($\sum$=25)		
Yes	14	56.0
No	11	44.0
NIH risk classification ($\sum$=35)		
Very low	0	0
Low	3	8.6
Intermediate	0	0
High	32	91.4

GISTs, gastrointestinal stromal tumors; density of tumor is determined by the imaging characteristics or pathological findings; KIT, c-KIT proto-oncogene protein; PDGFRA, platelet-derived growth factor receptor alpha; NIH, National Institutes of Health.

Tumors density was correlated with tumor size, and NIH risk classification (Table 2). A majority (84.2%) of tumors with the maximum diameter exceeding 10 cm, displayed mixed lesion (P = 0.002). Most high-risk tumors (77.4%) were presented with mixed lesion, whereas all low-risk tumors displayed solid lesion (P < 0.001).

Table 2
Relationship between tumor density and clinicopathologic features

Characteristics	Density of tumor			
	Solid	Cystic	Mixed	*P*
Age (y)(∑=36)				0.309
<55	2	3	10	
≥ 55	5	1	15	
Gender(∑=36)				0.382
Male	5	3	12	
Female	2	1	13	
Location(∑=36)				0.534
Left lobe	4	1	9	
Right lobe	3	3	9	
Caudate lobe	0	0	2	
Both lobe	0	0	5	
Size (cm)(∑=36)				0.002
0–2	1	0	0	
2.1-5	4	0	1	
5.1–10	2	1	8	
> 10	0	3	16	
Histological cell types(∑=30)				0.441
Spindle	4	3	15	
Epithelioid	1	0	0	
Mixed	2	1	4	
Mitotic index(∑=26)				0.079
≤ 5	4	1	4	
6.0–10	1	1	2	
> 10	0	1	12	

Density of tumor is determined by the imaging characteristics or pathological findings. KIT, c-KIT proto-oncogene protein; PDGFRA, platelet-derived growth; factor receptor alpha; NIH, National Institutes of Health.

Characteristics	Density of tumor			
	Solid	Cystic	Mixed	*P*
NIH risk classification($\sum$=34)				<0.001
Low	3	0	0	
High	3	4	24	

Density of tumor is determined by the imaging characteristics or pathological findings. KIT, c-KIT proto-oncogene protein; PDGFRA, platelet-derived growth; factor receptor alpha; NIH, National Institutes of Health.

Clinicopathological features were compared between 37 hepatic GISTs and 254 primary gastric GISTs (Table 3). Hepatic GISTs significantly differed from gastric GISTs in tumor size, main symptoms, histologic type, mitotic index, CD34 expression, NIH risk classification, and adjuvant therapy. Patients with hepatic GISTs displayed larger tumor size ($P < 0.001$), higher mitotic index ($P = 0.002$), more mixed morphology ($P = 0.012$) and higher risk classification ($P < 0.001$).

Table 3
Clinicopathologic features compared between gastric and hepatic GISTs.

Clinicopathologic features	Liver	Stomach	*P*
Age(∑=39)(y)			0.156
<55	16	80	
≥ 55	21	174	
Gender			0.321
Male	21	122	
Female	16	132	
The main symptoms			<0.001
Bleeding	1	25	
Abdominal mass	4	16	
Abdominal discomfort	7	108	
Bloating	5	25	
Nausea or loss of appetite	3	2	
Shortness of breath	3	1	
tiredness	2	9	
Size (cm)			<0.001
0–2	1	32	
2.1-5	5	91	
5.1–10	13	88	
> 10	18	43	
Histologic types			0.012
Spindle	23	232	
Epithelioid	1	2	
Mixed	7	20	
Mitotic index			0.002
≤ 5	9	158	

KIT, c-KIT proto-oncogene protein; PDGFRA, platelet-derived growth factor receptor alpha; NIH, National Institutes of Health.

Clinicopathologic features	Liver	Stomach	*P*
> 5	18	89	
Immunohistochemistry			
CD117(∑=34,250)	33	226	0.332
CD34(∑=30,248)	20	236	<0.001
Dog-1(∑=13,211)	11	182	0.868
Genetic mutation types			0.115
KIT	3	58	
PDGFRA	1	2	
Wild type	2	38	
Adjuvant therapy			0.024
Yes	14	45	
No	11	165	
NIH risk classification			<0.001
Very low	0	24	
Low	3	66	
Intermediate	0	75	
High	32	88	

KIT, c-KIT proto-oncogene protein; PDGFRA, platelet-derived growth factor receptor alpha; NIH, National Institutes of Health.

Diseases-free survival (DFS) time and disease-specific survival (DSS) time were compared between primary hepatic and gastric GISTs (Fig. 1). Patients were followed for a median period of 13.0 months (range: 1–189 months; mean: 32.4 months; Table 4). Survival data for DFS and DSS were significantly less favorable in patients with primary hepatic GISTs in comparisons to gastric GISTs (log-rank test, $P < 0.001$). 1-, 3-, 5-years DFS and DSS rate were 75.4%, 38.3%, 19.4% and 88.5%, 67.1%, 53.7% in patients with hepatic GISTs, respectively. 5-years DFS and DSS rate of hepatic GISTs were significantly worse than that of Gastric GISTs (19.4% vs 80.9%, $P < 0.001$; 53.7% vs 92.9%, $P < 0.05$). For patients with tumor size exceeding 5 cm or mitotic index exceeding 5/50 HPF, DFS and DSS were worse for those with primary hepatic GISTs ($P < 0.001$; Fig. 2, Fig. 3). Univariate and multivariable analysis showed location and NIH risk classification to be independent prognostic factors for DFS, and size and location were significantly associated with DSS (Table 5).

Table 4
Survival data for patients with hepatic GISTs

Survival data of cases of hepatic GISTs	
Characteristics	**Result**
Follow-up time	
Median (range)	13.0(1,189)
Mean ± SD	32.4 ± 46.4
Survival data	
Recurrence or Metastasis	10
GISTs-related death	7
1-/3-/5-year DFS rate (%)	75.4%/38.3%/19.4%
1-/3-/5-year DSS rate (%)	88.5%/67.1%/53.7%
DFS, disease-free survival time; DSS, disease-specific survival time; SD, standard deviation.	

Table 5
Prognostic factors for patients with GISTs (hepatic GISTs combined with gastric GISTs).

		Univariate Analysis			Multivariate Analysis		
	Prognostic Factors	β	HR(95% CI)	P	β	HR(95% CI)	*P*
DFS	Age	-0.019	0.981(0.440–2.184)	0.962			
	Gender	-0.386	0.680(0.321–1.438)	0.313			
	Size	0.945	2.573(1.591–4.160)	<0.001	0.291	1.338(0.635–2.820)	0.443
	Location	2.163	8.698(3.694–20.483)	<0.001	1.112	3.041(1.193–7.750)	**0.020**
	Histologic types	0.660	1.934(1.186–3.156)	0.008	0.285	1.330(0.665–2.661)	0.420
	NIH risk classification	1.309	3.704(1.971–6.960)	<0.001	1.418	4.131(1.953–8.736)	**<0.001**
	Adjuvant therapy	-0.929	0.395(0.168–0.927)	0.033	0.592	1.807(0.635–5.144)	0.267
	Mitotic index	1.577	4.842(2.104–11.142)	<0.001	0.457	1.580(0.558–4.468)	0.389
DSS	Age	-0.203	0.816(0.267–2.496)	0.722			
	Gender	0.066	1.068(0.356–3.204)	0.906			
	Size	1.187	3.279(1.544–6.964)	0.002	0.816	2.262(0.996–5.136)	**0.051**
	Location	2.656	14.239(4.511–44.951)	<0.001	1.880	6.557(1.773–24.250)	**0.005**
	Histologic types	0.890	2.436(1.251–4.744)	0.009	0.495	1.641(0.814–3.308)	0.166
	NIH risk classification	1.281	3.601(1.409–9.205)	0.007	0.172	1.187(0.252–5.581)	0.828
	Adjuvant therapy	-0.800	0.450(0.115–1.750)	0.249			

Prognostic factors for patients with hepatic and gastric GISTs, univariate and multivariable analysis of age, sex, size, location, histologic types, NIH risk classification, mitotic index, adjuvant therapy for disease-free survival (DFS) and disease-specific survival (DSS).

	Univariate Analysis			Multivariate Analysis		
Mitotic index	1.323	3.756(1.099–12.838)	0.035	0.502	1.652(0.416–6.562)	0.475

Prognostic factors for patients with hepatic and gastric GISTs, univariate and multivariable analysis of age, sex, size, location, histologic types, NIH risk classification, mitotic index, adjuvant therapy for disease-free survival (DFS) and disease-specific survival (DSS).

Discussion

As primary hepatic GISTs that occur outside the gastrointestinal tract are extremely rare, there was only one case in our database, which includes a total of 632 cases of GISTs from 2006 to 2019 (14 years). Most literature consists of case reports, or metastatic hepatic GISTs, with limited data. Compared to previous study (22 cases), the current study represents the largest number of hepatic GISTs consisting of 37 cases, and even evaluated the relationship between tumor density and clinicopathological features.[45] It implied that mitotic index exceeding 5/50 HPF or tumor size exceeding 5 cm was the important point to distinguish primary hepatic GISTs from gastric GISTs in DFS and DSS, which previous research had never reported. The result was also in accordance with the conclusion of modified NIH risk classification that gastric and non-gastric GISTs with tumor size less than 5 cm or mitotic indices less than 5/50 HPF shared the same risk classification (very low or low risk), however, for those with greater tumor sizes or higher mitotic index, non-gastric GISTs showed higher risk classification than gastric GISTs.

Recently, the ICC or ICC-like cells have been reported to exist in organs outside the gastrointestinal tract. Miettinen et al. described a primitive ancestor cell, present inside and outside of the intestines can give rise to GISTs and GIST-like extra-intestinal tumors, or that CD117 positive phenotype can be expressed in cells at inside and outside of the intestines.[46] Popescu et al. demonstrated that ICC-like cells occurred in human exocrine pancreas.[47] Ahmadia et al. confirmed that the Cajal cells were present in the extrahepatic bile ducts.[48] Fu et al. identified ICC-like cells in the liver.[49] Together, these studies imply the possibility of primary hepatic GISTs. Lack of specific clinical manifestations, the main symptoms were abdominal pain, discomfort, abdominal lesion, and abdominal distension. We report the positive expression of CD117 and CD34 was 97.1% and 66.7% in hepatic GISTs, which were in accordance with the results of previous studies about gastric GISTs (CD117, 95%; CD34, 70%).[50] The lesion distribution of hepatic GISTs included left lobe, right lobe and caudate lobe.

In the study, 25 cases (69.4%) showed mixed lesion and 4 cases (11.2%) showed cystic lesion. Mixed or cystic lesions of the liver are likely to be hepatic carcinoma, metastatic hepatic tumors, hepatic cyst, hepatic hemangioma, liver abscess, hepatic mucous cyst. The CT images of primary hepatic GISTs were similar to those of metastatic hepatic GISTs, presenting with heterogeneous hypodense lesions due to necrosis, hemorrhage and cystic degeneration of the mass. The CT image of our patient with heterogeneous hypodense mass was shown in Fig. 4. Majority studies demonstrated hepatic GISTs showed peripheral enhancement in the arterial phase and progressive concentric enhancement in the

portal venous phase.[45] Our report of primary hepatic GIST was consistent with previous study with progressive concentric enhancement in CT images. However, Hyum reported a case of primary hepatic GISTs showed the same degree of enhancement compared to live parenchyma in the arterial phase and persistent enhancement in the portal venous and delayed phase.[32] And he deemed GISTs were consisted of a wide range of pathologic spectrum, contributing to the discrepancy of different enhancement degree and pattern.

The present study even took consideration of the relationship between tumor density (solid, cystic and mixed lesion) and clinicopathological features, and discovered larger tumors were likely to display mixed density and tumors with mixed lesion were associated with high risk classification. Tumor density may be an indicator of risk classification for primary hepatic GIST. Size, mitotic count, anatomical location and rupture are important factors in evaluating the prognosis.[51] Larger tumors were likely to display mixed density, perhaps due to insufficient blood supply, leading to tumor necrosis or cystic degeneration. Tumors with mixed lesion were associated with high risk classification because of the connection between larger size and risk classification.

The radiological features of heterogenous hypodense and hypervascular nature of the tumor indicated hepatic GISTs, but also suggested other diagnoses, such as hepatocellular carcinoma. GISTs was definitively diagnosed by the histopathological examination of a tissue sample. The different cell morphology (spindle, epithelioid or mixed), distinctive immunohistochemical detection of CD117, CD34 and Dog-1 and molecular alterations features of *c-KIT* and *PDGFEA* genes mainly formed the diagnosis criteria of GIST. Li et al. demonstrated that (EUE-FNA) was the quickest and least painful way to obtain an accurate tissue diagnosis of hepatic GISTs.[44] However, because of the small amount of obtained tissue, diagnosing gene mutations status is difficult by this method and bleeding or implantation metastasis is possible. Most cases involving the study were diagnosis of primary hepatic GIST, by postoperative histopathological examination and few cases without operation were diagnosed by fine needle aspiration cytology.

Bleeding, bloating, abdominal discomfort, organ dysfunction and distant metastasis resulting in multiple organ failure were the main reasons for patients to seek for medical care. Compared with gastric GISTs, bleeding was less common in hepatic GISTs ($P < 0.001$) as well as spindle morphology ($P < 0.001$). Primary hepatic GISTs were most frequently newly diagnosed as higher risk than gastric GISTs (91.8% vs 34.8%, $P < 0.001$). Surgery was considered to be first-line therapy for resectable GISTs. R0 resections significantly improved survival of patients with primary hepatic GISTs and reduced postoperative recurrence rate.[52] It was reported extracorporeal hepatic resection and auto-transplantation (ECHRA) is an alternative method for tumors with large size, lesion extension or location adjacent to critical structures.[53–54] In our study, 25 patients had received R0 resection, and 5-years DFS and DSS rate were 19.4% and 53.7% in patients with follow-up data (19 patients), including one who underwent ECHRA and survived for 22 years, the longest disease-specific survival as far reported. ECHRA is likely to be a promising therapeutic strategy for large or awkwardly located hepatic GISTs with no metastasis.

Radiofrequency ablation was performed in 2 cases with very low risk classification, one case with 17 months of disease-free time. Otherwise, imatinib, a tyrosine kinase inhibitor against *c-KIT* and *PDGRA*, was widely used to treat unresectable GISTs, post-surgical relapses or metastases after surgery, or postoperative adjuvant therapy, which had been shown to improve survival of GISTs.[55] Efficacy of target therapy was associated with mutation status. Though wild type GISTs patients were treated with imatinib with a worse response, imatinib was also considered to improve the overall disease control rate (> 60%).[56–58] Sunitinib was recommended as a second-line treatment for recurrent, metastatic or unresectable GISTs and the first choice for generalized progression after standard-dose imatinib therapy. As non-gastric GISTs have higher risk of recurrence than gastric GISTs, 3 years of adjuvant therapy was recommended for patients suffered from hepatic GISTs with intermediate risk classification. The current study showed patients with intermediate or high risk classification received imatinib or sunitinib therapy only in 14 out of 25cases. Two patients received sunitinib therapy due to generalized progression under the standard dose and survived for 8 months and 53 months, respectively.

According to the NIH risk classification, gastric and non-gastric GISTs with tumor size less than 5 cm or mitotic index less than 5/50 HPF shared the same risk classifications (very low or low risk). However, for those with larger tumor sizes or mitotic index, non-gastric GISTs are higher risk than gastric GISTs. Our analysis of survival data associated with tumor size and mitotic index implied that with tumor size exceeding 5 cm or mitotic index exceeding 5/50 HPF, DFS and DSS were worse in patients with hepatic GISTs. The study implied than mitotic index exceeding 5/50 HPF or tumor size exceeding 5 cm may be the important factors to distinguish hepatic GISTs from gastric GISTs in DFS and DSS. Dematteo et al. found that tumor size, mitotic rate and location independently predicted recurrence after resection of primary stromal tumors.[59] And previous studies ever reported they were important malignant potential predictors of GIST.[60] Our multivariate analysis of prognostic factors of hepatic and gastric GISTs showed location and NIH risk classification to be independent prognostic factors for DFS and location and size were significantly associated with DSS. Compared with gastric GISTs, hepatic GISTs suffered from worse 5-year DFS rate (19.4% vs 80.9%, $P < 0.001$) and DSS rate (53.7% vs 92.9%, $P < 0.05$).

Our study has some limitations, mainly for its retrospective design and incomplete data collection. Firstly, the small hepatic GISTs sample size may have produced selection bias, leading to possible false-positive or -negative results. Secondly, we didn't make comparisons of survival data by tumor size less than 5 cm and mitotic index less than 5/50 HPF for limited data acquisition. Finally, we also did not perform subgroup analyzes of clinicopathological features and prognosis between hepatic and gastric GISTs, or between primary hepatic GISTs and other EGISTs, such as pancreas or omentum. Optimal treatment for hepatic GISTs should therefore be further studied.

Conclusion

Majority of primary hepatic GISTs share an immune profile of positive expression of CD117 and Dog-1, similar to that of gastric GISTs. The 37 hepatic GISTs and 254 gastric GISTs significantly differed in tumor size, main symptoms, histologic type, mitotic index, CD34 expression, NIH risk classification.

Compared with gastric GISTs, hepatic GISTs were obviously larger in size and showed higher mitotic index. Mitotic index exceeding 5/50 HPF or tumor size exceeding 5 cm may be the critical factor to distinguish hepatic GISTs from gastric GISTs in DFS and DSS.

Abbreviations

GISTs: gastrointestinal stromal tumors;

PDGFRA: platelet-derived growth factor receptor alpha;

CKNI: China National Knowledge Infrastructure;

IHC: immunohistochemistry;

NIH: National Institutes of Health;

DFS: Diseases-free survival;

DSS: disease-specific survival;

ICC: Cajal cells;

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XX searched and reviewed the literature, designed the research and wrote the paper. ZGL designed the research and provided the clinical data. ZZC participated in reviewing the literature, designing the research, revising and writing the paper.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Liao Ning Cancer Hospital.

Consent for publication

Written informed consents for publication were obtained from the patients in our center.

Competing of interest

There were no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Figures

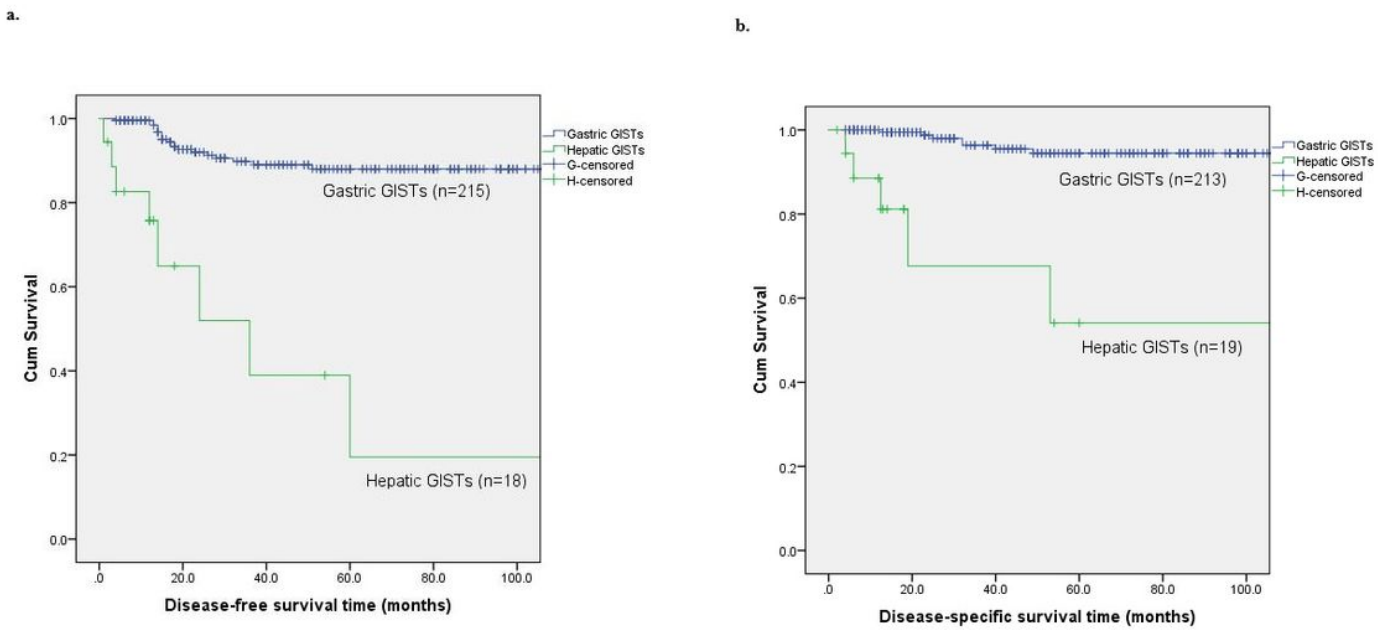

Figure 1

Comparisons of survival data between gastric and hepatic GISTs. Kaplan-Meier survival analysis was employed to compare difference between groups. a. The comparison of DFS in patients with hepatic and gastric GISTs, P < 0.001. b. The comparison of DSS in patients with hepatic and gastric GISTs, P < 0.001.

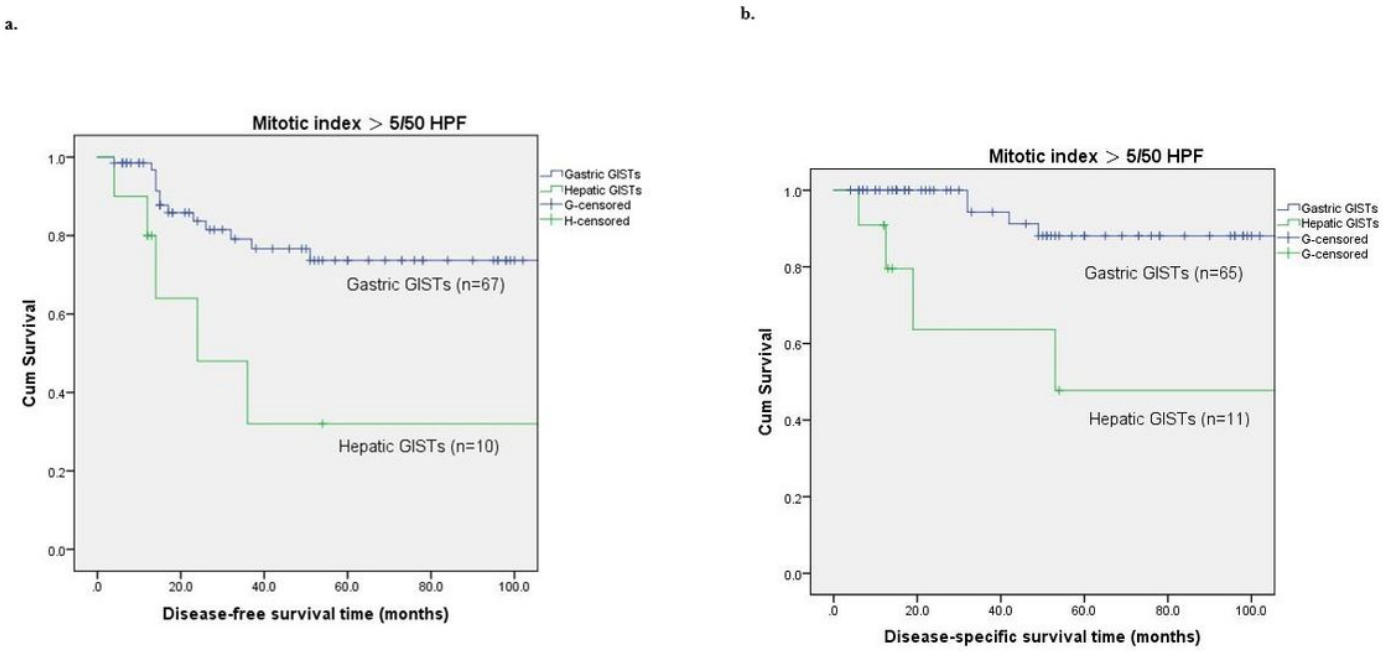

Figure 2

Comparisons of disease-free survival and disease-specific survival associated with mitotic index between gastric and hepatic GISTs. Kaplan-Meier survival analysis was employed to compare difference between groups. a. Comparison of disease-free survival associated with mitotic index exceeding 5/50 HPF

between gastric and hepatic GISTs, P = 0.027. b. Comparison of disease specific survival associated with mitotic index exceeding 5/50 HPF between gastric and hepatic GISTs, P < 0.001.

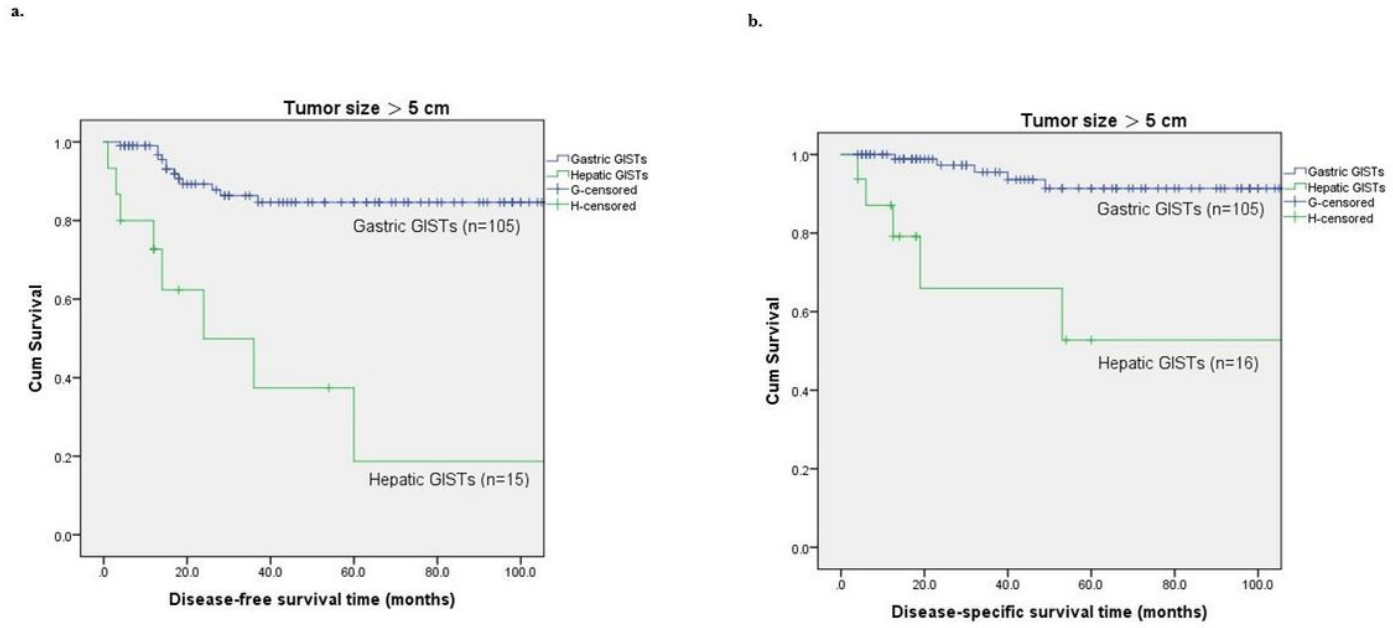

Figure 3

Comparisons of disease-free survival and disease-specific survival associated with tumor size between gastric and hepatic GISTs. Kaplan-Meier survival analysis was employed to compare difference between groups. a. Comparison of disease-free survival associated with tumor size exceeding 5 cm between gastric and hepatic GISTs, P < 0.001. b. Comparison of disease specific survival associated with mitotic index exceeding 5 cm between gastric and hepatic GISTs, P < 0.001.

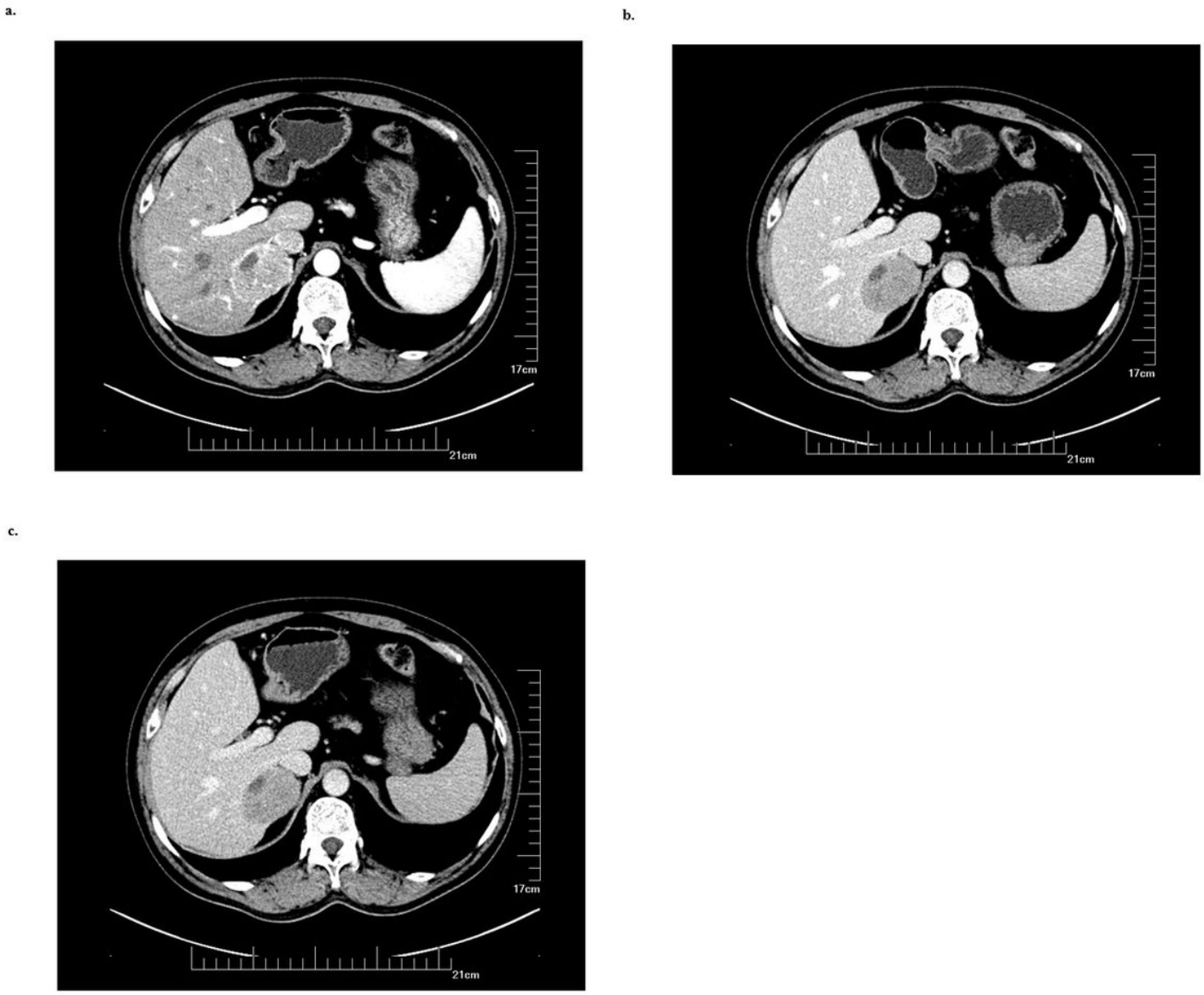

Figure 4

The computed tomography scan showed a heterogenous hypodense mass with a maximum diameter of 5.2cm in the right posterior lobe of the live. a. CT images showed peripheral enhancement in the arterial phase. b and c. Progressive concentric enhancement in the portal venous and delayed phase.