Original Article

Association of tumor morphology with long-term prognosis after liver resection for patients with a solitary huge hepatocellular carcinoma—a multicenter propensity score matching analysis

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Background: A solitary hepatocellular carcinoma (HCC) without macrovascular invasion and distant metastasis, regardless of tumor size, is currently classified as early-stage disease by the latest Barcelona Clinic Liver Cancer (BCLC) staging system. While the preferred treatment is surgical resection, the association of tumor morphology with long-term survival outcomes after liver resection for a solitary huge HCC of ≥10 cm has not been defined.

Methods: Patients who underwent curative liver resection for a solitary huge HCC were identified from a multicenter database. Preoperative imaging findings were used to define spherical- or ellipsoidal-shaped lesions with smooth edges as balloon-shaped HCCs (BS-HCCs); out-of-shape lesions or lesions of any shape with matt edges were defined as non-balloon-shaped HCCs (NBS-HCCs). The two groups of patients with BS-HCCs and NBS-HCCs were matched in a 1:1 ratio using propensity score matching (PSM). Clinicopathologic characteristics, long-term overall survival (OS) and recurrence-free survival (RFS) were assessed.

Results: Among patients with a solitary huge HCC, 74 pairs of patients with BS-HCC and NBS-HCC were matched. Tumor pathological features including proportions of microvascular invasion, satellite nodules, and incomplete tumor encapsulation in the BS-HCC group were lower than the NBS-HCC group. At a median follow-up of 50.7 months, median OS and RFS of all patients with a solitary huge HCC after

PSM were 27.8 and 10.1 months, respectively. The BS-HCC group had better median OS and RFS than the NBS-HCC group (31.9 *vs.* 21.0 months, P=0.01; and 19.7 *vs.* 6.4 months, P=0.015). Multivariate analyses identified BS-HCC as independently associated with better OS (HR =0.592, P=0.009) and RFS (HR =0.633, P=0.013).

Conclusions: For a solitary huge HCC, preoperative imaging on tumor morphology was associated with prognosis following resection. In particular, patients with BS-HCCs had better long-term survival following liver resection versus patients with large NBS-HCCs.

Keywords: Hepatocellular carcinoma (HCC); survival; recurrence; tumor morphology; hepatectomy

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer with an estimated incidence of >1 million cases by 2025 (1). Surgery, in the form of liver resection or liver transplantation, remains the mainstay of treatment aimed at cure for patients with resectable diseases (2). The Barcelona Clinic Liver Cancer (BCLC) classification has been endorsed as the optimal staging system and treatment algorithm for HCC by the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) (3,4). Since first being proposed, the BCLC classification has been updated several times with the most notable update being staging of large solitary HCC >5 cm. In the latest BCLC staging, solitary HCC, without vascular invasion and distant metastasis, regardless of tumor size is classified as early-staged HCC (BCLC stage 0/A). In turn, the recommended treatment is liver resection for patients having preserved liver functions (5). However, surgical resection for a solitary large (>5 cm) or huge (>10 cm) HCC remains a challenge even for experienced hepatic surgeons, with an increased risk of massive intraoperative hemorrhage and fatal postoperative complications (6-9). Good surgical decision-makings require comprehensive evaluations to balance expected survival benefits with potential surgical difficulty and risks (10-12). Therefore, good understanding of the clinicopathological characteristics and prognostic factors of patients being considered for liver resection of a solitary huge HCC, even those considered as early-staged HCC by the BCLC staging system, is important.

Pathological features relating to tumor biology and invasiveness associated with long-term oncologic prognosis have been identified in previous studies on liver resection for a solitary large or huge HCC (13-15). These features include tumor differentiation (16,17), tumor encapsulation (18,19), microvascular invasion (14,20), and satellite nodules (20). Data on morphologic shape are scarce. Of note, most HCCs start to grow in the early stages in a spherical or ellipsoidal shape. As tumor size increases, more aggressive tumor features can manifest with loss of smooth tumor edges, breakthrough of the tumor envelope, loss in original spherical or ellipsoidal shapes, presence of satellites or multiple nodules around the primary tumors, micro- and macrovascular invasion, and distant metastases (21,22). However, one specific type of solitary huge HCC that exhibits low invasive and metastatic potentials, and may have more favorable outcomes after curative resection has been described (*Figure 1*). In particular, a solitary huge HCC, despite its size of >5 cm for a solitary large HCC and >10 cm for a solitary huge HCC, that retains its spherical or ellipsoidal shape, smooth tumor edge, absence of local protrusion, and intact capsule or pseudocapsule has been suggested to have a better prognosis. This type of HCC is named "balloon-shaped" HCC based on its shape.

Although solitary large or huge HCCs have been reported to have specific molecular characteristics (14,23,24), to our knowledge, no study has focused on the prognostic significance of tumor morphology among patients with solitary huge HCC after curative liver resection. In the current study, data on the clinicopathologic characteristics, preoperative computed tomography (CT) and/or magnetic resonance imaging (MRI) features, and perioperative and postoperative survival outcomes from a multicenter cohort of patients with solitary huge HCCs without macrovascular invasion and distant metastases were retrospectively analyzed. Using propensity score matching

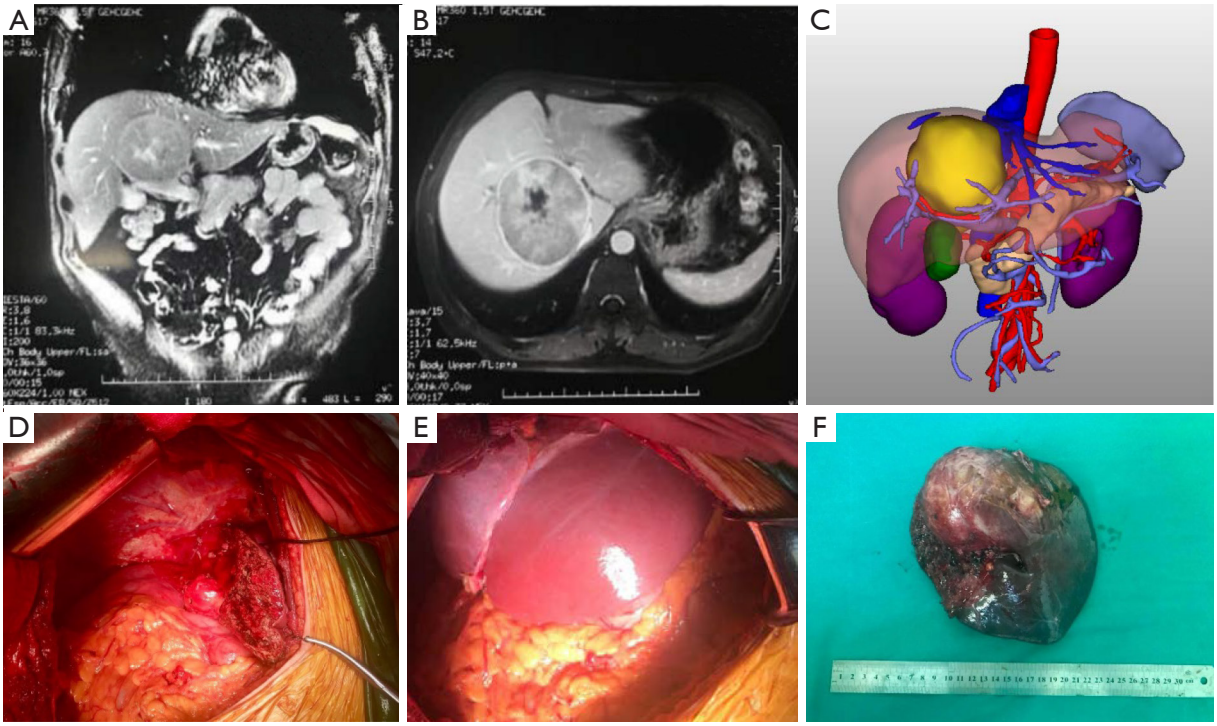


Figure 1 A representative set of MRI, three-dimensional imaging, and operative photographs of a 45-year-old male with a solitary huge BS-HCC located between the left and right hemilivers. MRI (A,B) and three-dimensional imaging (C) show a solitary huge lesion located in segments 4, 5, and 8 (largest tumor size: 11.0 cm). The preoperative AFP was 48.9 ng/mL. This patient underwent curative extended right hepatectomy (D-F) on November 02, 2017, and was still alive and recurrence-free at the last follow-up on July 20, 2021. MRI, magnetic resonance imaging; BS-HCC, balloon-shaped hepatocellular carcinoma; AFP, alpha-fetoprotein.

(PSM), long-term survival and recurrence outcomes were compared between patients with balloon shaped-HCCs (BS-HCC) versus non-balloon-shaped HCCs (NBS-HCC) on survival outcomes after liver resection. In particular, we sought to define whether tumor morphology could be used to stratify patients with solitary huge HCCs over 10 cm in diameter relative to prognosis following resection. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-423/rc).

Methods

Patients

Using a multicenter database from 11 Chinese hospitals [Eastern Hepatobiliary Surgery Hospital (EHBH) of Shanghai, Changzheng Hospital of Shanghai, Liuyang People's Hospital, Ziyang First People's Hospital, Fourth Hospital of Harbin, First Affiliated Hospital of Nantong University, Fuyang People's Hospital, Meizhou People's Hospital, Zhejiang Provincial People's Hospital, First Affiliated Hospital of Harbin Medical University, and Pu'er People's Hospital], patients who underwent curative-intent liver resection for newly diagnosed HCC from June 2007 to August 2020 were retrospectively reviewed. Approval was obtained from the Institutional Review Boards of these hospitals. The inclusion criteria were patients with: (I) a solitary HCC with a maximum diameter of 10 cm or more; (II) absence of macrovascular invasion and distant metastasis; (III) curative liver resection with complete removal of all microscopic and macroscopic tumors (R0 resection); (IV) adequate preoperative contrast-enhanced CT or MRI images, clinicopathological variables and follow-up data. The exclusion criteria were patients with: (I) age younger than 18 years; (II) multiple HCCs; (III) tumors with a maximum diameter <10 cm; (IV) preoperative anti-HCC treatment; (V) palliative liver resection, including microscopically positive (R1 resection) or grossly positive

(R2 resection) resection margins; (VI) unavailable data on preoperative CT/MRI or essential prognostic variables; (VII) loss to follow-up within 6 months after surgery. Data were collected in both a prospective and retrospective fashion depending on the data field. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and the Ethical Guidelines for Clinical Studies for the enrolled centers. Informed consent was waived by the Institutional Review Board of EHBH (No. EHBHKY2019-K-005). Consent for the relevant procedures and the use of data for research purposes were obtained from all the patients before treatment.

Identifications of imaging features between BS-HCC and NBS-HCC

The digital data on all the preoperative CT and/or MRI images carried out within 1 month before surgery of all the enrolled patients from the participating hospitals other than EHBH were sent to EHBH. The images were independently reviewed by one radiologist (HB) and two surgeons (XXF and YLQ) who were blinded to patient clinicopathological information. Lesions were subsequently categorized as BS-HCC or NBS-HCC. Any discrepancies in classification were settled through discussion until a consensus was reached. According to preoperative imaging findings, a solitary huge BS-HCC had all the following features: (I) a spherical- or ellipsoidal-shaped lesion larger than 10 cm; (II) smooth tumor edges without any local protrusion; and (III) a low- or high-density peripheral rim around the lesion. In contrast, out-of-shape lesions or lesions of any shape with matt edges on imaging were classified as NBS-HCCs.

Clinicopathological variables and perioperative outcomes

The medical records were retrospectively reviewed for clinicopathological variables. Preoperative clinical characteristics included age, sex, American Society of Anesthesiologists (ASA) score, hepatitis B virus infection, liver fibrosis, cirrhosis, Child-Pugh grading, preoperative platelets count, and preoperative alpha-fetoprotein (AFP) level. Preoperative imaging, data on tumor size, tumor location (involving one or both hemi-livers), tumor morphology (balloon type or non-balloon type), and tumor growing mode (pedunculated or not) were recorded. Perioperative outcomes included intraoperative blood loss, intraoperative blood transfusion, extent of hepatectomy (minor or major), type of hepatectomy (anatomical or non-anatomical), and postoperative 30-day mortality and morbidity. Major hepatectomy was defined as resection of three or more Couinaud liver segments. Anatomical hepatectomies were defined by the Brisbane 2000 nomenclature of liver anatomy (25), while non-anatomical hepatectomies included wedge resection or limited resection.

Postoperative pathological features collected relative to the liver and tumor included cirrhosis, microvascular invasion, satellite nodules, tumor encapsulation (no/incomplete or complete), tumor differentiation (poor or well/moderate), and resection margin (<1 or ≥1 cm). Tumor encapsulation was defined as the presence of a fibrous sheath around the tumor on gross inspection (18). Tumor differentiation was identified using the Edmondson-Steiner histopathological grading system (26). Pedunculated HCC reflected a special growth pattern of HCC with more than 50% of tumor volume protruding outside of liver parenchyma.

Study endpoints

Given that the study focused on the prognostic role of tumor morphology among patients with a solitary huge HCC who underwent curative liver resection, the primary endpoints were overall survival (OS) and recurrence-free survival (RFS); secondary endpoints included incidence of death and recurrence on follow-up. Tumor recurrence was clinically suspected with progressive elevation of serum AFP levels and ultrasonographic detection of a new hepatic lesion. The diagnosis of a recurrence was made when dynamic CT scan or MRI demonstrated contrast enhancement in the arterial phase and wash-out in the venous phase, or when hepatic angiography disclosed a high tumor vascularity. Patients developing recurrence were treated with re-resection, local ablation, liver transplantation, transcatheter arterial chemoembolization, radiotherapy, targeted therapy, or supportive care, depending on the patterns of recurrence, liver functional reserve, and patient general conditions. Re-resection, liver transplantation, and local ablation were defined as potentially curative treatments, while other treatments were deemed as noncurative treatments. OS was calculated from the date of liver resection to either the date of death or the date of the last follow-up, while RFS was calculated from the date of liver resection to the date of diagnosis of first recurrence, or the date of death or the last follow-up.

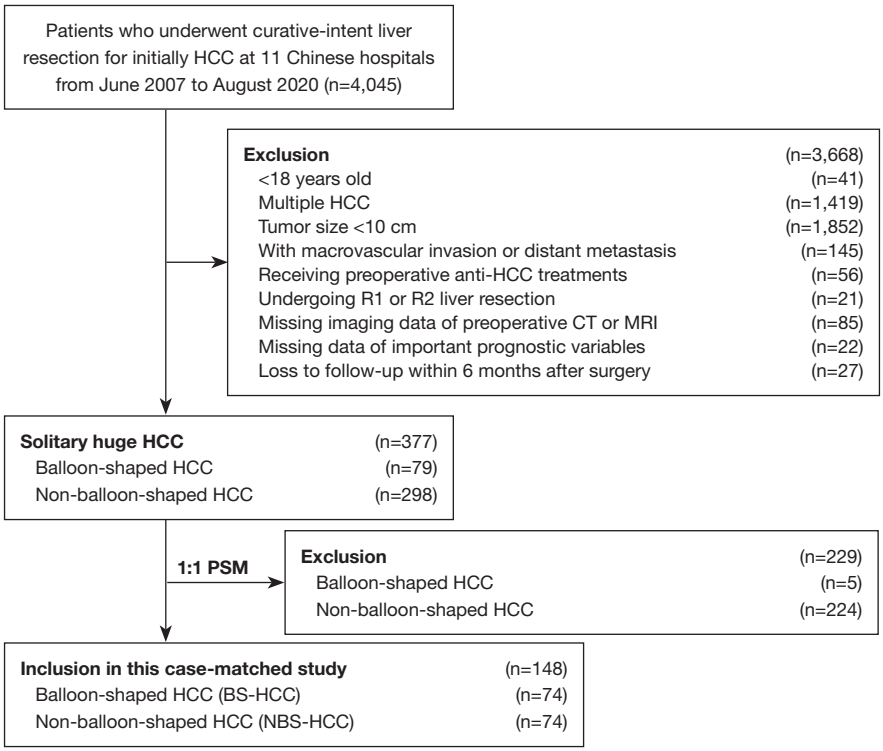


Figure 2 Flow chart of the study. HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; PSM, propensity score matching.

Statistical analysis

Clinicopathological characteristics were summarized using frequency and percentage for categorical variables and mean ± standard deviation (SD) or median (range) for continuous variables. The χ^2 test or Fisher's exact test was used to compare categorical covariates, while continuous covariates were compared using the independent-samples *t*-test or Mann-Whitney U test between the PSM patients with BS-HCC and NBS-HCC. OS and RFS were calculated by the Kaplan-Meier methods and compared by the log-rank test. The univariate and multivariate Cox proportional hazard regression model was used to identify independent prognostic factors of OS and RFS. Variables with a P<0.10 on univariate analysis were subjected to the multivariate Cox-regression model using a forward stepwise variable selection. Statistical analyses were performed using the SPSS software version 25.0 (SPSS, Chicago, IL, USA). A two-tailed P value of <0.05 was considered statistically significant for all the tests.

Results

Among patients who underwent resection for a solitary huge HCC, an initial analysis of variance and χ^2 test for baseline demographics and preoperative imaging characteristics of patients demonstrated differences in certain variables, including Child-Pugh grading, tumor size, and uni- or bilateral hemi-liver location among patients with BS-HCC versus NBS-HCC. Using propensity scores to adjust for these 4 variables, a 1:1 PSM was conducted to create matched study cohorts of BS-HCC (n=74) and NBS-HCC (n=74) patients (*Figure 2*). The typical CT or MRI imaging findings of these 148 patients are displayed in the Figures S1,S2.

Clinicopathological variables and perioperative outcomes

Comparison of clinicopathologic characteristics and perioperative outcomes between the BS-HCC and NBS-HCC groups are noted in *Table 1*. In the overall cohort, there were 122 (82.4%) men and 26 (17.6%) women with a mean age ± SD of 51.0±12.4 years. The mean ± SD tumor diameter was 12.1±1.9 cm. There were 48 (32.4%) patients who had an HCC located between the left and right hemi-livers (bilateral hemi-liver location); 43 (29.1%)

Table 1 Clinicopathologic characteristics and perioperative outcomes after liver resection for patients with a solitary huge hepatocellular carcinoma

Variables	Total (n=148)	BS-HCC (n=74)	NBS-HCC (n=74)	P
Demographic characteristics				
Age, years*	51.0±12.4	52.0±12.6	50.0±12.3	0.339
Male sex	122 (82.4)	59 (79.7)	63 (85.1)	0.388
ASA score >2	16 (10.8)	9 (12.2)	7 (9.5)	0.597
HBV (+)	132 (89.2)	64 (86.5)	68 (91.9)	0.290
Fibrosis	136 (91.9)	67 (90.5)	69 (93.2)	0.547
Cirrhosis	93 (62.8)	46 (62.2)	47 (63.5)	0.865
Child-Pugh grade B	16 (10.8)	8 (10.8)	8 (10.8)	1.000
Preoperative platelets count, $\times10^9$/L*	187±80	192±85	183±74	0.472
Preoperative AFP >400 μg/L	81 (54.7)	38 (51.4)	43 (58.1)	0.409
Preoperative imaging characteristics				
Bilobular location	48 (32.4)	26 (35.1)	22 (29.7)	0.482
Tumor size, cm*	12.1±1.9	12.0±1.9	12.3±1.9	0.343
Pedunculated growing	43 (29.1)	23 (31.1)	20 (27.0)	0.587
Postoperative tumor pathological features				
Microvascular invasion	81 (54.7)	30 (40.5)	51 (68.9)	0.001
Satellite nodules	59 (39.9)	18 (24.3)	41 (55.4)	<0.001
Incomplete tumor encapsulation	102 (68.9)	37 (50.0)	65 (87.8)	<0.001
Poor tumor differentiation	128 (86.5)	61 (82.4)	67 (90.5)	0.149
Resection margin <1 cm	94 (63.5)	48 (64.9)	46 (62.2)	0.733
Perioperative outcomes				
Intraoperative blood loss >600 mL	42 (28.4)	18 (24.3)	24 (32.4)	0.274
Intraoperative blood transfusion	45 (30.4)	19 (25.7)	26 (35.1)	0.211
Major hepatectomy	75 (50.7)	35 (47.3)	40 (54.1)	0.411
Anatomical hepatectomy	56 (37.8)	28 (37.8)	28 (37.8)	1.000
Postoperative 30-day mortality	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Postoperative 30-day morbidity	68 (45.9)	33 (44.6)	35 (47.3)	0.741
Major morbidity (Clavien-Dindo III–V)	27 (18.2)	15 (20.3)	12 (16.2)	0.523
Minor morbidity (Clavien-Dindo I–II)	41 (27.7)	18 (24.3)	23 (31.1)	0.358
Postoperative complications				
Hepatic dysfunction	15 (10.1)	7 (9.5)	8 (10.8)	0.785
Abdominal hemorrhage	3 (2.0)	2 (2.7)	1 (1.4)	1.000
Bile leakage	5 (3.4)	3 (4.1)	2 (2.7)	1.000

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=148)	BS-HCC (n=74)	NBS-HCC (n=74)	P
Incisional infection	10 (6.8)	5 (6.8)	5 (6.8)	1.000
Organ/space infection	9 (6.1)	5 (6.8)	4 (5.4)	1.000
Respiratory infection	2 (1.4)	2 (2.7)	0 (0.0)	0.497
Pleural effusion	45 (30.4)	19 (25.7)	26 (35.1)	0.211
Ascites	19 (12.8)	7 (9.5)	12 (16.2)	0.219
Others	16 (10.8)	8 (10.8)	8 (10.8)	1.000

*, values are mean ± standard deviation. ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; BS-HCC, balloon-shaped hepatocellular carcinoma; NBS-HCC, non-balloon-shaped hepatocellular carcinoma.

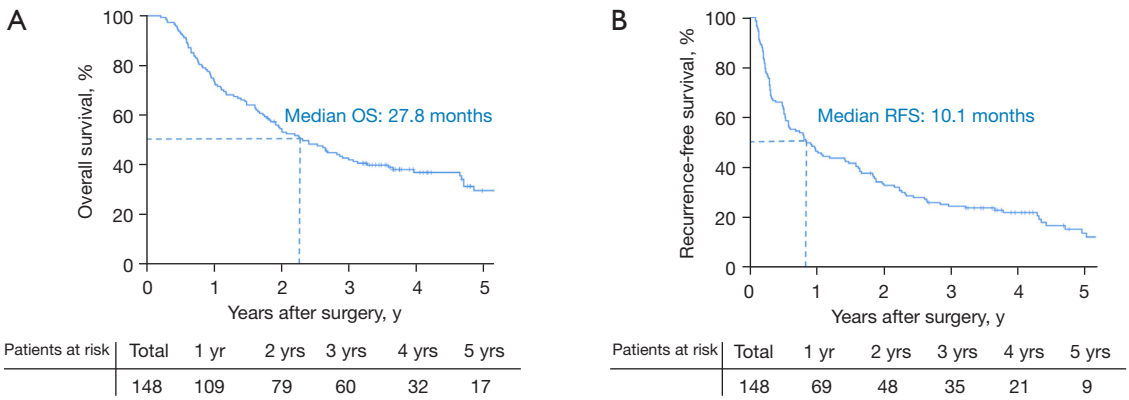


Figure 3 Curves of OS (A) and RFS (B) after liver resection for patients with a solitary huge HCC. OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma.

patients had pedunculated-growing HCCs. There were no differences in demographic and preoperative imaging characteristics between the 2 groups of patients. There were also no differences in tumor differentiation and resection margin status between the groups. The incidence of microvascular invasion (40.5% *vs.* 68.9%, P=0.001), satellite nodules (24.3% *vs.* 55.4%, P<0.001), and incomplete tumor encapsulation (50.0% *vs.* 87.8%, P<0.001) was different among patients with BS-HCC, as these patients had lower incidence of these adverse clinical factors than patients with NBS-HCC.

There was no postoperative 30-day death, however, the postoperative 30-day morbidity was 45.9%. There were no differences existed in likelihood of intraoperative blood transfusion, major hepatectomy, anatomical hepatectomy, postoperative 30-day morbidity, and postoperative complications (all P>0.05).

Long-term outcomes

At a median follow-up of 50.7 [95% confidence interval (CI), 42.2–59.2] months, HCC recurrence and death occurred in 118 (79.7%) and 104 (70.3%) patients in the overall cohort, respectively. Median OS and RFS were 27.8 (95% CI: 21.0–34.6) months and 10.1 (95% CI: 5.7–14.5) months, respectively (*Figure 3*). Postoperative recurrence and death among patients with NBS-HCC were higher versus patients with BS-HCC (86.5% *vs.* 73.0%, P=0.041, and 83.8% *vs.* 56.8%, P<0.001, respectively) (*Table 2*). The 1-, 3-, and 5-year OS among patients with BS-HCC was 79.7%, 49.3%, and 44.8% (median OS: 31.9 months), respectively, which were better than patients with NBS-HCC (67.6%, 35.1%, and 21.1%, respectively; median OS: 21.0 months, P=0.010, *Figure 4A*). The 1-, 3-, and 5-year RFS among patients with BS-HCC versus NBS-HCC were 56.8%,

Table 2 Long-term outcomes after liver resection for patients with a solitary huge hepatocellular carcinoma

Variables	Total (n=148)	BS-HCC (n=74)	NBS-HCC (n=74)	P
Period of follow-up, months*	62.9±3.3	53.9±3.7	76.1±5.6	<0.001
Postoperative adjuvant TACE	21 (14.2)	8 (10.8)	13 (17.6)	0.239
Initial recurrence at follow-up	118 (79.7)	54 (73.0)	64 (86.5)	0.041
Intrahepatic	95 (64.2)	44 (59.5)	51 (68.9)	0.230
Extrahepatic	6 (4.1)	2 (2.7)	4 (5.4)	0.677
Intra- & extrahepatic	17 (11.5)	8 (10.8)	9 (12.2)	0.797
Death at follow-up	104 (70.3)	42 (56.8)	62 (83.8)	<0.001
Cancer-specific death	86 (58.1)	34 (45.9)	52 (70.3)	0.038
Non-cancer-specific death	18 (12.2)	8 (10.8)	10 (13.5)	0.615
Median OS, 95% CI, months	27.8 (21.0–34.6)	31.9 (19.9–43.9)	21.0 (12.3–29.7)	0.010
1-year OS rate, %	73.6	79.7	67.6	
3-year OS rate, %	42.1	49.3	35.1	
5-year OS rate, %	29.8	44.8	21.1	
Median RFS, 95% CI, months	10.1 (5.7–14.5)	19.7 (9.3–30.1)	6.4 (3.5–9.3)	0.015
1-year RFS rate, %	46.6	56.8	36.5	
3-year RFS rate, %	24.7	29.1	20.3	
5-year RFS rate, %	14.0	19.8	9.7	

*, values are mean ± standard deviation. TACE, transcatheter arterial chemoembolization; OS, overall survival; CI, confidence interval; RFS, recurrence-free survival; BS-HCC, balloon-shaped hepatocellular carcinoma; NBS-HCC, non-balloon-shaped hepatocellular carcinoma.

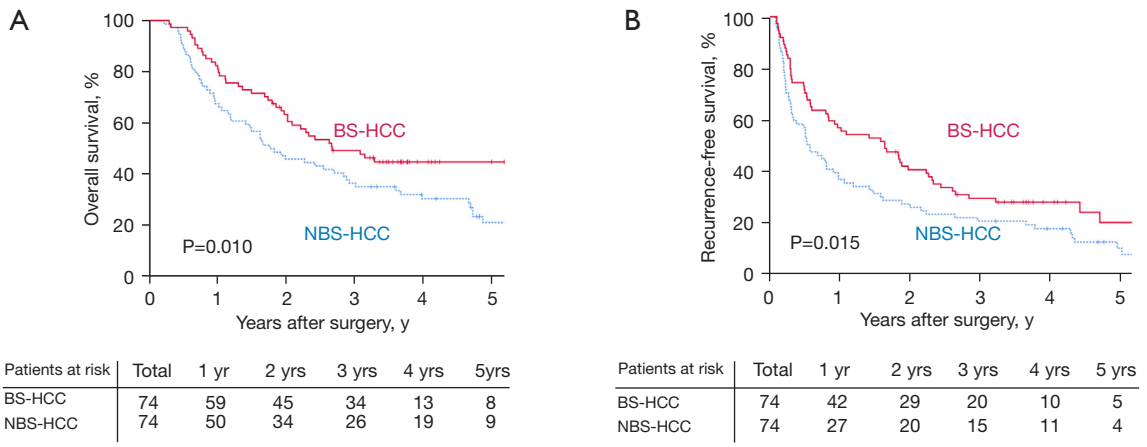
29.1%, and 19.8% *vs.* 36.5%, 20.3% and 9.7%, respectively (median RFS: 19.7 *vs.* 6.4 months, *Figure 4B*) (P=0.015).

Univariate and multivariate Cox-regression demonstrated several factors associated with OS and RFS following liver resection among patients with a solitary huge HCC (*Table 3* and *Table 4*). In particular, on multivariate analyses after controlling for other clinical factors, BS-HCC remained independently associated with better OS [hazard ratio (HR) =0.592; 95% CI: 0.399–0.878; P=0.009] and RFS (HR =0.633; 95% CI: 0.441–0.909; P=0.013) versus NBS-HCC following curative-intent liver resection for a solitary huge HCC.

Discussion

Over the past several decades, liver resection for HCC has gradually evolved to become a safe procedure with a low perioperative mortality of less than 3% at most centers and even as low as 0% at a few large hepatic centers. However, long-term survival outcomes remain unsatisfactory mainly because of the high incidences of postoperative recurrence and metastasis (27-29). Biological characteristics based on tumor size, nodularity, encapsulation, and differentiation have prognostic significance after liver resection of solitary large/huge HCC (13-20). In our study, compared with patients who had NBS-HCC, patients with BS-HCC had better OS and RFS outcomes after curative liver resection of a solitary huge HCC. On multivariate analysis, balloon-shaped tumors as identified on preoperative imaging (spherical- or ellipsoidal-shaped lesions with smooth edges) remained an independent predictive factor associated with better OS and RFS after curative liver resection for solitary huge HCC. Collectively, the data support the hypothesis that tumor morphology was an important predictor of long-term survival outcomes after curative liver resection. Thus, patients with BS-HCC should be considered for liver resection regardless of size if technically operable.

Although the results of this study found that OS and RFS in patients with NBS-HCC were both worse than those with BS-HCC, it did not mean that there



Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5yrs
BS-HCC	74	59	45	34	13	8
NBS-HCC	74	50	34	26	19	9

Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
BS-HCC	74	42	29	20	10	5
NBS-HCC	74	27	20	15	11	4

Figure 4 Comparison curves of OS (A) and RFS (B) after liver resection for a solitary huge HCC between patients with BS-HCC and NBS-HCC. BS-HCC, balloon-shaped hepatocellular carcinoma; NBS-HCC, non-balloon-shaped hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival.

should be any difference in the surgical indications and surgical methods between them. In our opinion, for a solitary huge HCC, if hepatectomy is carried out with curative intent and with insurance in safety, it is worth active consideration. However, in view of the significant differences in postoperative recurrence and survival outcome between patients with BS- and NBS-HCC, postoperative surveillance for recurrence should be enhanced for patients with NBS-HCC, such as shortening the surveillance interval. In addition, despite the lack of a widely recognized neoadjuvant and adjuvant treatment regimen, potentially effective treatments against recurrence are worth considering for patients with NBS-HCC, such as pre- or postoperative TACE, neoadjuvant or adjuvant systemic therapy, etc.

In several previous studies, Yang *et al.* defined a special type of HCC (a solitary large HCC with tumor size >5 cm) had better long-term survival outcomes after hepatectomy. Interesting, these types of tumors had a lower expression of genes associated with HCC invasion and metastatic potentials (14,30-32). In the present study, the independent impact of tumor morphology on long-term oncologic prognosis after curative resection for solitary huge HCC of >10 cm was analyzed. The result demonstrated that BS-HCC, a specific type of HCC with a balloon shape, had much more favorable survival outcomes with less aggressive biologic characteristics and behavior than the NBS-HCC. *Table 1* demonstrates that patients with NBS-HCCs had a higher proportion of microvascular invasion, incomplete tumor encapsulation, and satellite nodules. These data supported the aggressive behavior of NBS-HCC with this tumor morphology. As a tumor capsule is composed of thick collagen fibers and vascular structures, complete tumor encapsulation has been recognized as a protective barrier in confining the tumor and preventing spread of tumor cells (33,34). Encapsulated HCCs have also been correlated with lower incidence of aggressive tumor characteristics like microvascular invasion and satellite nodules, and better OS and RFS outcomes after liver resection (18,33).

In this study, the classification of balloon or non-balloon shape was based on preoperative CT or MRI imaging within 1 month before surgery. Of note, HCCs with different shapes are not hard to distinguish on imaging. In particular, in the current study, a radiologist and two surgeons who participated in the imaging evaluations were able to reach agreement in over 90% of cases on initial assessment. The definition of "balloon-shaped" was determined based on spherical or ellipsoidal shape, as well as a low- or high-density shadow around the intact tumor capsule. In the entire cohort of 377 patients before PSM, unanimous judgement on identification of BS or NBS was reached on imaging in almost all the patients (N=358, 95.0%), and discrepancies on the judgement of low- or high-density peripheral rim around the lesion existed only in 19 cases (5.0%). However, after discussion, a consensus was easily and completely reached for these 19 cases. To test the impact of these 19 cases, further sensitivity analysis was made, and the conclusions did not change. In the BS-HCC group, the proportion of specimens with complete tumor encapsulation on postoperative histopathological

Table 3 Univariate and multivariate Cox-regression analysis predicting overall survival after liver resection of patients with a solitary huge hepatocellular carcinoma

Variables	HR comparison	UV		MV	
		HR (95% CI)	P*	HR (95% CI)	P*
Age	>60 *vs.* ≤60 years	1.032 (0.657–1.622)	0.890		
Sex	Male *vs.* female	1.400 (0.809–2.422)	0.229		
ASA score	>2 *vs.* ≤2	1.243 (0.647–2.390)	0.514		
HBV (+)	Yes *vs.* no	0.860 (0.458–1.616)	0.639		
Cirrhosis	Yes *vs.* no	1.102 (0.736–1.650)	0.637		
Child-Pugh grade	B *vs.* A	1.372 (0.766–2.456)	0.287		
Preoperative platelets count	>100 *vs.* ≤100×10^9/L	1.143 (0.638–2.049)	0.653		
Preoperative AFP level	>400 *vs.* ≤400 μg/L	2.060 (1.375–3.085)	<0.001	NA	0.369
Tumor shape	BS-HCC *vs.* NBS-HCC	0.602 (0.406–0.891)	0.011	0.592 (0.399–0.878)	0.009
Tumor location	Bilobular *vs.* unilobular	0.837 (0.559–1.253)	0.386		
Tumor size	>12.0 *vs.* ≤12.0 cm	1.901 (1.268–2.850)	0.002	1.981 (1.311–2.994)	0.001
Pedunculated growing	Yes *vs.* no	0.964 (0.633–1.469)	0.865		
Microvascular invasion	Yes *vs.* no	1.445 (0.974–2.146)	0.068	NA	0.406
Satellite nodules	Yes *vs.* no	1.484 (1.009–2.184)	0.045	NA	0.462
Tumor encapsulation	Incomplete *vs.* complete	1.982 (1.246–3.153)	0.004	NA	0.334
Tumor differentiation	Poor *vs.* well/moderate	1.077 (0.602–1.929)	0.802		
Resection margin	<1 *vs.* ≥1 cm	1.652 (1.087–2.511)	0.019	1.596 (1.048–2.431)	0.030
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.831 (1.223–2.740)	0.003	NA	0.134
Intraoperative blood transfusion	Yes *vs.* no	1.854 (1.247–2.757)	0.002	NA	0.114
Extent of hepatectomy	Major *vs.* minor	1.312 (0.890–1.934)	0.170		
Type of hepatectomy	Non-anatomical *vs.* anatomical	1.001 (0.673–1.489)	0.995		
Postoperative TACE	Yes *vs.* no	0.665 (0.376–1.177)	0.162		

*, variables with P<0.1 in univariate analysis were subjected to multivariate Cox-regression model using forward stepwise variable selection. ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; HR, hazard ratio; BS-HCC, balloon-shaped hepatocellular carcinoma; NBS-HCC, non-balloon-shaped hepatocellular carcinoma; UV, univariate; MV, multivariate; CI, confidence interval; NA, not available; TACE, transcatheter arterial chemoembolization.

examination was 50%, which was much higher than the NBS-HCC group (only 12.2%, P<0.001). On univariate analysis, patients with complete tumor encapsulation had better OS and RFS than patients with incomplete tumor encapsulation (P=0.004 and 0.015). Although whether tumor encapsulation is complete or incomplete can only be confirmed by postoperative histopathological examination of resected specimens, preoperative imaging findings can be used in its prediction.

Interestingly, a large proportion of patients with resectable solitary huge HCCs, including the balloon or non-balloon types, had pedunculated growth tumors (29.1%, 43/148) (i.e., half of the tumors protruded from the surfaces of the livers, it is common for small HCCs to have a capsule). When HCC tumors grow rapidly, there may be increasingly more pressure exerted by the surrounding liver

Table 4 Univariate and multivariate Cox-regression analysis predicting recurrence-free survival after liver resection of patients with a solitary huge hepatocellular carcinoma

Variables	HR comparison	UV		MV	
		HR (95% CI)	P*	HR (95% CI)	P*
Age	>60 *vs.* ≤60 years	1.161 (0.761–1.771)	0.488		
Sex	Male *vs.* female	1.363 (0.835–2.225)	0.215		
ASA score	>2 *vs.* ≤2	1.307 (0.719–2.378)	0.380		
HBV (+)	Yes *vs.* no	1.082 (0.607–1.929)	0.788		
Cirrhosis	Yes *vs.* no	1.023 (0.709–1.476)	0.903		
Child-Pugh grade	B *vs.* A	1.145 (0.656–1.998)	0.635		
Preoperative platelets count	>100 *vs.* ≤100×10^9/L	1.216 (0.718–2.060)	0.467		
Preoperative AFP level	>400 *vs.* ≤400 μg/L	1.490 (1.040–2.133)	0.030	NA	0.079
Tumor shape	BS-HCC *vs.* NBS-HCC	0.644 (0.450–0.922)	0.016	0.633 (0.441–0.909)	0.013
Tumor location	Bilobular *vs.* unilobular	1.247 (0.856–1.816)	0.250		
Tumor size	>12.0 *vs.* ≤12.0 cm	1.665 (1.143–2.426)	0.008	1.628 (1.111–2.385)	0.012
Pedunculated growing	Yes *vs.* no	0.902 (0.611–1.332)	0.603		
Microvascular invasion	Yes *vs.* no	1.331 (0.927–1.909)	0.121		
Satellite nodules	Yes *vs.* no	1.359 (0.949–1.945)	0.094	NA	0.842
Tumor encapsulation	Incomplete *vs.* complete	1.649 (1.104–2.464)	0.015	NA	0.405
Tumor differentiation	Poor *vs.* well/moderate	1.100 (0.640–1.891)	0.730		
Resection margin	<1 *vs.* ≥1 cm	1.631 (1.116–2.385)	0.012	1.669 (1.136–2.451)	0.009
Intraoperative blood loss	>600 *vs.* ≤600 mL	1.819 (1.241–2.665)	0.002	NA	0.989
Intraoperative blood transfusion	Yes *vs.* no	1.718 (1.181–2.499)	0.005	1.803 (1.224–2.654)	0.003
Extent of hepatectomy	Major *vs.* minor	1.071 (0.750–1.528)	0.707		
Type of hepatectomy	Non-anatomical *vs.* anatomical	0.950 (0.656–1.375)	0.785		
Postoperative TACE	Yes *vs.* no	0.749 (0.441–1.271)	0.284		

*, variables with P<0.1 in univariate analysis were subjected to multivariate Cox-regression model using forward stepwise variable selection. ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; HR, hazard ratio; BS-HCC, balloon-shaped hepatocellular carcinoma; NBS-HCC, non-balloon-shaped hepatocellular carcinoma; UV, univariate; MV, multivariate; CI, confidence interval; NA, not available; TACE, transcatheter arterial chemoembolization.

parenchyma on the HCC if it is centrally located in the liver versus a peripherally located tumor. Thus, there is a higher tendency for a centrally located tumor to break through the constraints of a capsule or pseudo-capsule to obtain the required growth space than a peripherally located HCC. Once breaking through the capsule, the tumor may grow uncontrollably and become irregular in shape. As a result, the chances of microsatellite lesions and the development of multiple secondary lesions can greatly increase. In pedunculated HCCs that often arise in peripherally located areas, these lesions are technically easier to resect with lower incidence of postoperative recurrence, and better long-term survival (35,36). Of note, the chance of tumor rupture for pedunculated HCCs is higher, as one study reported that among 143 patients with ruptured HCC reported 35% were pedunculated in nature (37).

All patients in our cohort underwent open hepatectomy, and none of them underwent minimally invasive hepatectomy (laparoscopic or robotic). Till now, minimally invasive hepatectomy for huge HCC is still controversial,

although some studies have reported that huge HCC was not a contraindication for minimally invasive hepatectomy, and the perioperative morbidity and mortality rates were comparable to those of open hepatectomy (38,39). In our experience, laparoscopic hepatectomy for huge HCCs is full of challenges and difficulties, and the probability of intraoperative tumor rupture, especially if carried out by surgeons who are not very experienced in laparoscopic surgery. More prospective observational studies and even randomized clinical trials are needed to further determine the safety and efficacy of minimally invasive hepatectomy to compare with open hepatectomy for huge HCC. Currently, radiomics and machine learning are hot research topics, which have shown great application value in diagnosis, prognosis, treatment selection and monitoring of response to treatment for malignant tumors, including HCC (40-42). We have already stated on research on prognostic evaluation for solitary huge HCC by using these technologies.

Several limitations need to be considered when interpreting data from the current study. As a retrospective study, there may be inherent residual biases despite PSM. The vast majority (nearly 90%) of patients also had HBV-related HCC. As such, external validation in a Western cohort of patients in which HCV and alcoholism are the main etiological causes of HCC is needed. In addition, the current multi-institutional study did not allow for standardization of protocols related to liver resection technique. Furthermore, all operations were performed by experienced surgeons at large specialized surgical centers in China who had experience in managing HCC patients. In turn, the results may not be generalizable in small centers or to less experienced surgeons.

Conclusions

In conclusion, the data demonstrated that liver resection can safely and effectively be performed in patients with a solitary huge HCC >10 cm, with reasonably good median OS and RFS rates. Preoperative imaging categorization of tumor morphology was an important prognostic factor relative to long-term OS and RFS outcomes following curative-intent resection of HCC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-423/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-423/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-423/coif). TMP and WYL serve as the unpaid editorial board members of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and the Ethical Guidelines for Clinical Studies for the enrolled centers. Informed consent was waived by the Institutional Review Board of EHBH (No. EHBHKY2019-K-005). Consent for the relevant procedures and the use of data for research purposes were obtained from all the patients before treatment.

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Supplementary

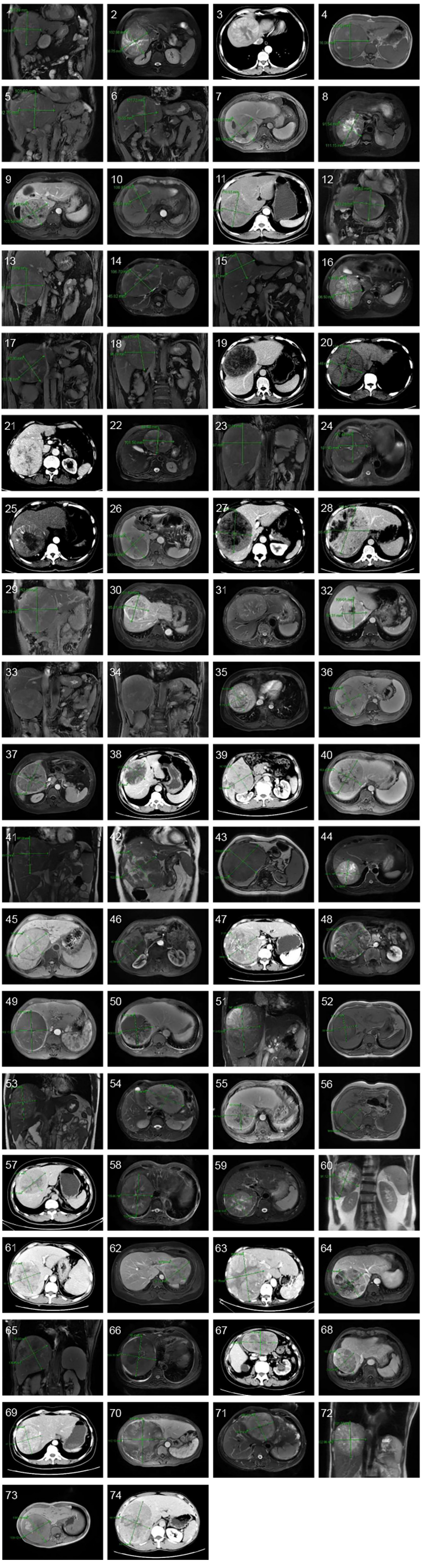

Figure S1 Balloon-shaped Solitary Huge HCC.

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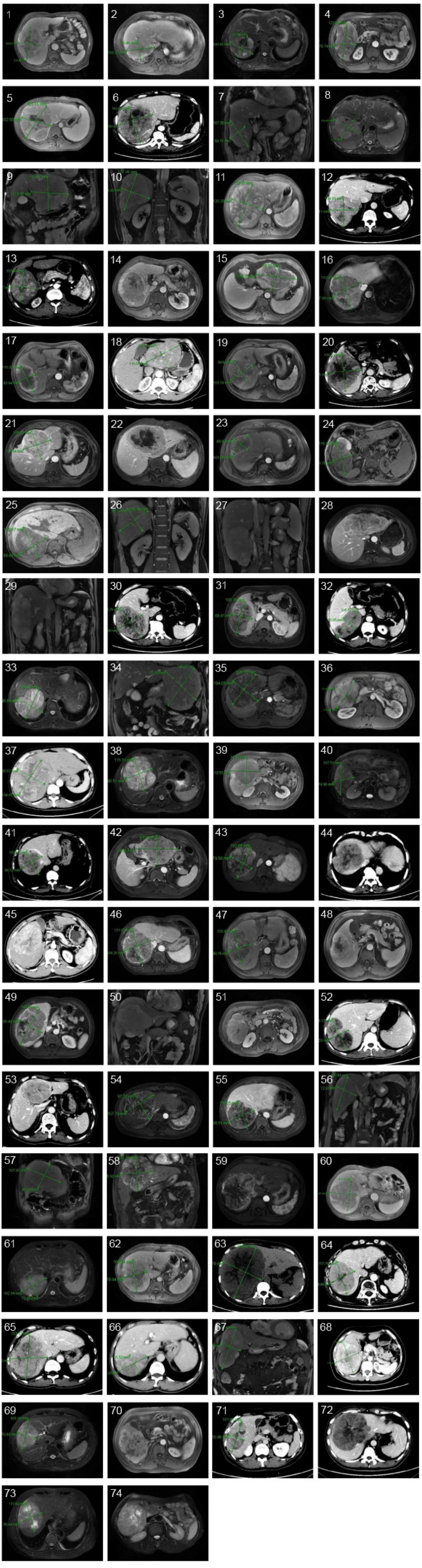

Figure S2 Non-balloon-shaped Solitary Huge HCC.

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