High-Intensity Focused Ultrasound Ablation for Unresectable Primary and Metastatic Liver Cancer: Real-World Research in a Chinese Tertiary Center With 275 Cases

Yongshuo Ji, Junqiu Zhu, Linglin Zhu, Yanfei Zhu and Hong Zhao *

HIFU Center of Oncology Department, Huadong Hospital Affiliated to Fudan University, Shanghai, China

This retrospective analysis was conducted to evaluate the feasibility and safety of high-intensity focused ultrasound ablation for primary liver cancer and metastatic liver cancer. Patients with liver cancer who received high-intensity focused ultrasound were included in this analysis, including a primary liver cancer cohort (n=80) and a metastatic liver cancer cohort (n=195). The primary endpoint of our research was tumor response. The secondary endpoints included survival outcomes, visual analog scale pain scores, alpha-fetoprotein relief, and complications. Objective response rate and disease control rate were observed to be 71.8% and 81.2%, respectively, in patients with primary liver cancer and were 63.7% and 83.2% in cases with metastatic liver cancer. Alpha-fetoprotein levels and visual analogue scale levels significantly decreased after treatment compared with the baseline levels in patients with primary liver cancer (p<0.05). Median overall survival was estimated to be 13.0 and 12.0 months in the primary liver cancer and metastatic liver cancer cohorts. The 1-year survival rate was 70.69% and 48.00%, respectively. Multivariate regression analysis showed that visual analogue scale $\geq$ 5, longest diameter $\geq$ 5 cm, and portal vein invasion were the independent risk factors for poor survival in primary liver cancer. For patients with metastatic liver cancer, independent risk factors were identified as visual analogue scale $\geq$ 5, longest diameter $\geq$ 5 cm, existence of extrahepatic metastases, existence of portal vein invasion, and time to high-intensity focused ultrasound treatment from diagnosis < 3 months. Severe adverse events were rarely reported. In conclusion, high-intensity focused ultrasound might be an effective and safe option for patients with liver cancer regardless of primary and metastatic lesions.

Keywords: HIFU, hepatocellular carcinoma, metastatic hepatic carcinoma, response, pain, survival, biomakers

INTRODUCTION

Liver cancer is one of the most common diseases worldwide (1, 2) with estimated deaths ranking fourth among all kinds of cancers (1). Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancer with steadily rising incidence globally (3, 4). The majority of diagnosed cases of HCC have advanced disease (5), which might cause the poor prognosis. The disease often presents in the setting of advanced cirrhosis, and orthotropic liver transplant provides the greatest chance for both cure and long-term survival (6, 7).

Metastatic liver cancer (MLC) is more prevalent than primary liver cancer (PLC) but no less harmful (8, 9). Liver metastases commonly arise from gastrointestinal cancers, including those of the esophagus, stomach, pancreas, and colorectum, as well as from other solid tumors (10). It is reported that liver metastasis accounts for about 25% of all metastatic disease (11).

The local treatment of hepatic metastases is based on surgical interventions. Surgery is the first choice for the treatment of both primary and secondary liver cancer. However, it is feasible in only 20%–30% of cases (12). Local, nonsurgical options for liver cancer treatment include radiofrequency ablation, transarterial radioembolization and chemoembolization, electroporation, cryotherapy, laser therapy, and various radiotherapy methods (13, 14). Nevertheless, these techniques have multiple limitations (i.e., a traumatic puncture of the parenchyma, the limited size of lesions, and an inability to real-time monitor during the treatment) (15, 16).

High-intensity-focused-ultrasound (HIFU) is an emerging, noninvasive ablation procedure that can ablate various solid tumors, including primary and secondary liver cancer. It can focus ultrasound energy on the lesions of interest and induce tumor coagulative necrosis by thermal effect (17). The promising efficacy of HIFU for HCC has been demonstrated by numbers of studies in spite of high heterogeneity between studies (18). HIFU monotherapy (19–33) could achieve great tumor response with 1-year survival rates of approximately 80%. When combined with transarterial chemoembolization (TACE) (34–42), the results were roughly equal to that of HIFU monotherapy. HIFU local therapy for MLC patients has also been evaluated by several clinical trials (20, 24, 43–47). The response rate was also high—up to about 80%—with the survival outcome remaining unknown. However, these studies included very small sample sizes, and a considerable number of studies are even fewer than 10 patients. We have previously reported the efficacy of HIFU in the treatment of PLC (48) without the results of MLC. However, some limitations of our previous research, such as earlier enrollment with a small sample size and simplicity of the results, prompted us to update the results of HIFU treatment for PLC cases.

We conducted this retrospective analysis with a relatively large sample size to reveal the real-world clinical benefit and safety of HIFU treatment for PLC and MLC cases. Our focus was to determine the response status after HIFU treatment in patients with PLC and MLC. For response evaluation by HIFU ablation, we compared response evaluation criteria in solid tumors (RECIST) 1.1 and modified RECIST (mRECIST)

criteria. We also endeavored to determine which factors could affect the response status and survival outcomes. We report results of primary endpoints of objective response rate (ORR) and disease control rate (DCR) as well as secondary outcomes, including overall survival (OS) with 1-year survival rates, pain relief rate, alpha-fetoprotein (AFP) response rate, and adverse events (AEs).

MATERIALS AND METHODS

Patients

Two hundred seventy-five patients who were histologically confirmed with unresectable HCC or MLC in our center from January 2013 to August 2018 were consecutively included in this retrospective analysis. The diagnosis of HCC or MLC is pathologically proven, and the diagnosis of HCC is made by pathology/cytology or according to the American Association for the Study of Liver Diseases (AASLD) (2010) diagnostic criteria (49). The eligibility criteria were as follows: (1) 18 years of age or older; (2) adequate organ function (white blood cell $\geq 3.9 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, bilirubin ≤ 2mg/dL; hemoglobin ≥ 10g/dL, and serum creatinine ≤ 150mmol/L); (3) Child-Pugh class A-B; (4) life expectancy of ≥ 3 months; (5) prior liver resection, radiotherapy, or chemotherapy allowed; and (6) received at least one post-HIFU response evaluation. The exclusion criteria were as follows: (1) patients who are indicated for liver resection, (2) women with pregnancy or lactation, (3) patients with a previous cerebrovascular event and active infectious disease, (4) patients with clinically significant liver failure (i.e., encephalopathy or ascites found clinically), and (5) patients who received thrombolytic therapy or other anticoagulant therapy within 4 weeks.

This study was approved by the ethics committee of Huadong Hospital and was done following the Declaration of Helsinki. All patients signed a document of informed consent.

HIFU Treatment

HIFU ablation was performed using the HIFUINT-9000 system (Shanghai A&S Sci-Tec Co., LTD, Shanghai, China), which is a B-mode ultrasound-guided device (**Figure 1**) (50). The patient was fasted to gas-producing food 3 days before treatment and banned water in the morning of the treatment day. During treatment, the patient was placed in the supine position without antibiotics or anesthesia. First, the tumor location, size, and morphological characteristics were identified by computed tomography (CT), b-mode sonography, or magnetic resonance imaging (MRI). Meanwhile, the influence of the tumor on adjacent organs and blood vessels was also evaluated. Next, the detecting head of this system completed the relocalization of the therapy area. Finally, the ablation energy focus was controlled to move along with a three-dimensional axis until it covered the target lesions. The input power was 5–10 kW/cm^2, and therapy depth was 2–15 cm. The practice-focused sphere was 3 x 3 x 8 mm. The unit ultrasonic pulse included transmit
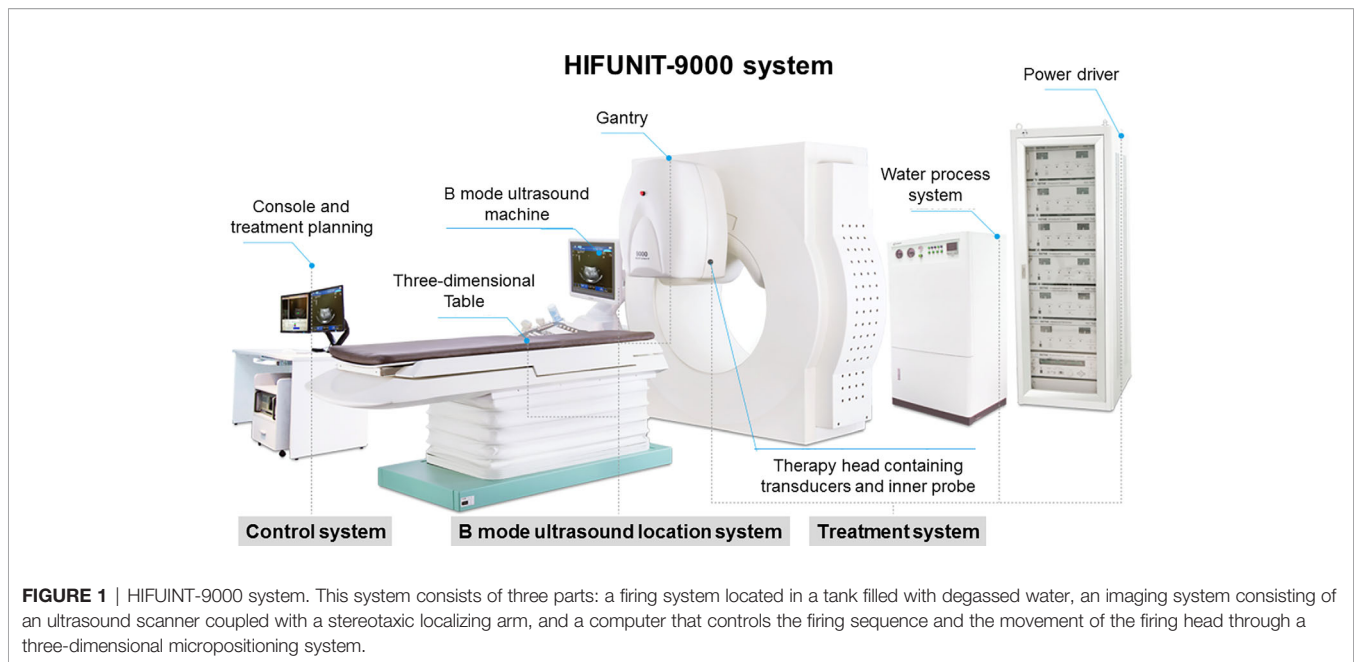
FIGURE 1 | HIFUINT-9000 system. This system consists of three parts: a firing system located in a tank filled with degassed water, an imaging system consisting of an ultrasound scanner coupled with a stereotaxic localizing arm, and a computer that controls the firing sequence and the movement of the firing head through a three-dimensional micropositioning system.

time of 200 ms and intermission time of 400 ms, respectively. Each focused sphere needs the ultrasonic pulse 8–10 times. The average treatment and sonication time was about 30 minutes and 10 minutes, respectively. All of the parameters were allowed to be varied depending on the depth of the tumor.

Observation and Measurement

The primary endpoints were the ORR with duration of response (DOR) and DCR in the overall cohort and PLC and MLC, respectively. The secondary endpoints were OS with 1-year survival rates, pain relief rate, AFP response rate, and safety. The assessments of hepatic lesions were done with a CT or MRI scan at baseline, 1 month, 3 months, 6 months, and 12 months after HIFU ablation. The RECIST 1.1 (51) and mRECIST (52) were separately used to assess the tumor response at 1 month after HIFU treatment and followed at 2 months. ORR = [(complete response (CR) + partial response (PR)]/total x 100%, and DCR = [(CR+PR +stable disease (SD)]/total x 100%. Visual analogue scale (VAS) value was used as the indicator of pain. HIFU-related AEs were recorded, and the severity was graded by the CTCAE, version 4 (53).

Statistical Analysis

All the data analyses were conducted using the statistical software of STATA Version 11.0 (College Station, TX, USA). Our data were described as the mean ± SD for normally distributed data or median with range for non-normally distributed data. OS analysis of patients was conducted by the Kaplan-Meier method. Potential independent risk factors for survival were evaluated by univariate analysis (log-rank test) and multivariate analysis (Cox proportional hazards model). P-value < 0.05 indicated statistical significance.

RESULTS

Baseline Characteristics

According to the inclusion criteria, 275 patients were included finally, including 85 cases with HCC and 190 cases with MLC. The baseline characteristics of these cases are listed in **Table 1**. The cohort of HCC consisted of 54 and 31 cases with Stage III and Stage IV, in which 19 cases (22.4%) had intrahepatic metastasis. For patients with MLC, the common primary tumor sites were colon (n=43, 22.6%), pancreas (n=42, 22.1%), stomach (n=29, 15.3%), rectum (n=17, 8.9%), breast (n=17, 8.9%), gallbladder (n=10, 5.3%), and others, which were fewer than 10 cases. There were 58 (30.5%) that were synchronous (diagnosed concomitantly or within 3 months of the primary tumor) and 132 (69.5%) that were metachronous, in which 52 cases (27.4%) were diagnosed beyond 1 year of the former tumor. AFP levels of HCC and MLC groups were 639.3 ± 106.8 µg/L and 182.7 ± 37.2 µg/L with positive rates of 77.6% and 13.2%, respectively. Histories of hepatitis B (45.9% vs. 3.7%) and liver cirrhosis (22.4% vs. 0.7%) were more common in patients with HCC compared with patients with MLC. VAS ≥ 5 was also more commonly seen (40% vs. 6.3%) in the HCC group than the MLC group.

ORR and DCR

All 275 cases received a response evaluation by mRECIST and RECIST 1.1 criteria, respectively. The CR rate, ORR, and DCR were estimated to be 53.8% (95% CI = 47.9–59.7%), 66.2% (95% CI = 60.6–71.8%), and 82.5% (95% CI = 78.0–87.1%) by mRECIST. However, when RECIST 1.1 was used, no CR was identified, and ORR and DCR were 31.3% (95% CI = 23.3–38.7%) and 71.6% (95% CI = 64.2–77.9%), respectively, which were also significantly lower than the rates by mRECIST

TABLE 1 | Baseline characteristics of patients and tumors.

Characteristics	PLCn=85	MLCn=190	OverallN=275
Age			
Median (range), year	63 (37-89)	63 (31-89)	63 (31-89)
<65, n (%)	48 (56.5)	102 (53.7)	150 (54.5)
≥65, n (%)	37 (43.5)	88 (46.3)	125 (45.5)
Gender			
Male, n (%)	69 (81.2)	111 (58.4)	180 (65.5)
Female, n (%)	16 (18.8)	79 (41.6)	95 (34.5)
ECOG PS			
Median (range)	2 (0-4)	2 (0-4)	2 (0-4)
<2, n (%)	46 (54.1)	77 (40.5)	123 (44.7)
≥2, n (%)	39 (45.9)	113 (59.5)	152 (55.3)
VAS			
Median (range)	5 (0-10)	1 (0-7)	3 (0-10)
< 5, n (%)	51 (60.0)	178 (93.7)	229 (83.3)
≥ 5, n (%)	34 (40.0)	12 (6.3)	46 (16.7)
Lesions number			
Median (range)	3 (1-6)	3 (1-7)	3 (1-7)
Single, n (%)	16 (18.8)	29 (15.3)	45 (16.4)
Multiple, n (%)	69 (81.2)	161 (84.7)	230 (83.6)
LDi*			
Mean (± SE), cm	4.94 (± 1.67)	5.37 (± 1.90)	138 (50.2)
< 5 cm, n (%)	51 (60.0)	87 (45.8)	137 (49.8)
≥ 5 cm, n (%)	34 (40.0)	103 (54.2)	
Portal vein invasion			
Yes, n (%)	33 (38.8)	44 (23.2)	77 (28.0)
No, n (%)	52 (61.2)	146 (76.8)	198 (72.0)
Tumor location			
Right lobe, n (%)	7 (8.2)	14 (7.4)	21 (7.6)
eft lobe, n (%)	18 (21.2)	24 (12.6)	42 (15.3)
Both, n (%)	60 (70.6)	152 (80.0)	212 (77.1)
Stage of PLC		NA	NA
Stage III	54 (63.5)		
Stage IV	31 (36.5)		
Intrahepatic metastasis status		NA	NA
Yes, n (%)	19 (22.4)		
No, n (%)	66 (77.6)		
Extrahepatic metastases status			
Yes, n (%)	22 (25.9)	70 (36.8)	92 (33.5)
No, n (%)	63 (74.1)	120 (63.2)	183 (66.5)
Liver metastases present at initial diagnosis	NA		NA
Median time&, month (range)		6 (0-132)	
Yes (synchronous), n (%)		58 (30.5)	
No (metachronous), n (%)		132 (69.5)	
< 12 months		80 (42.1)	
≥ 12 months		52 (27.4)	
Primary tumor site for MLC	NA		NA
Colon, n (%)		43 (22.6)	
Pancreas, n (%)		42 (22.1)	
Gastric, n (%)		29 (15.3)	
Rectum, n (%)		17 (8.9)	
Breast, n (%)		17 (8.9)	
Gallbladder, n(%)		10 (5.2)	
Others†		32 (16.8)	
Histories of disease			
Hepatitis B, n (%)	39 (45.9)	7 (3.7)	46 (16.7)
Liver cirrhosis, n (%)	19 (22.4)	1 (0.5)	20 (7.3)
Hypertension, n (%)	17 (20.0)	29 (15.3)	46 (16.7)
Diabetes Mellitus, n (%)	10 (11.8)	17 (8.9)	27 (9.8)

(Continued)

TABLE 1 | Continued

Characteristics	PLCn=85	MLCn=190	OverallN=275
Prior therapies for liver cancer			
Median (range)	1 (0-3)	0 (0-3)	0 (1-3)
Prior ≥one therapies, n (%)	14 (16.5)	6 (3.2)	20 (7.3)
Prior surgery, n (%)	13 (15.9)	5 (2.6)	18 (6.5)
Prior RFA, n(%)	2 (2.4)	1 (0.5)	3 (1.1)
Prior TACE, n (%)	1 (1.2)	0	1 (0.4)
Prior chemotherapy, n (%)	1 (1.2)	1 (0.5)	2 (0.7)
AFP level			
Mean (± SE), µg/L	639.3 (± 106.8)	182.7 (± 37.2)	323.83
Negative (< 400 µg/L), n (%)	19 (22.4)	165 (86.8)	(± 71.3)
Positive (≥ 400 µg/L), n (%)	66 (77.6)	25 (13.2)	184 (66.9)
			91 (33.1)
Time to HIFU#			
Median (range), months	3 (0.5-83)	3 (0.5-24)	3 (0.5-83)
< 3, n (%)	40 (47.1)	93 (48.9)	133 (48.4)
≥ 3, n (%)	45 (52.9)	97 (51.1)	142 (51.6)
HIFU sessions			
Median (range), months	5 (2-40)	5 (2-40)	5 (2-40)
< 5, n (%)	14 (16.5)	47 (24.7)	61 (22.2)
≥ 5, n (%)	71 (83.5)	143 (75.3)	214 (77.8)
Indicated for RFA			
Yes, n (%)	40 (47.1)	81 (42.6)	121 (44.0)
No, n (%)	45 (52.9)	109 (57.4)	154 (56.0)

LDis for the patients with multiple lesions were the sum of the longest diameter of all these lesions.

#Time to HIFU ablation from the diagnosis of HCC.

&Median time of liver metastases from initial diagnosis.

†Others included lung cancer (n=8), esophagus cancer (n=5), renal cancer (n=3), nasopharynx cancer (n=3), melanoma (n=3), cervical cancer (n=2), bladder cancer (n=2), ovarian cancer (n=1), prostatic cancer (n=1), skin cancer (n=1), unknown (n=3).

AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, Hepatocellular Carcinoma; HIFU, High-Intensity Focused Ultrasound; PLC, primary liver cancer; RFA, radiofrequency ablation; LDi, longest diameter; MLC, metastatic liver cancer; NA, not applied; TACE, transarterial chemoembolization; VAS, visual analogue scale.

(p=0.001). The results were described as PLC and MLC separately with subgroup analyses (**Table 2**).

According to the mRECIST criteria, 63.5% (95% CI = 53.1–74.0) of patients with HCC achieved CR after HIFU ablation (**Figure 2**) with an ORR of 71.8% (95% CI = 62.0–81.5) and DCR of 81.2% (95% CI = 72.7–89.7), respectively. The CR rate, ORR, and DCR were 49.5% (95% CI = 42.3–56.6), 63.7% (95% CI = 56.8–70.6), and 83.2% (95% CI = 77.8–88.5), respectively, in patients with MLC.

No CR was observed by RECIST 1.1 in cases with both HCC and MLC. For patients with HCC, 32.9% (95% CI = 22.7–43.1%) of cases were responding to HIFU ablation, and 74.1% (95% CI = 64.6–83.6%) of cases obtained disease control. The ORR and DCR were 30.5% (95% CI = 23.9–37.1%) and 70.5% (95% CI = 64.0–77.1%), respectively, in patients with MLC.

Chi-square tests revealed that the Eastern Cooperative Oncology Group performance status (ECOG PS), VAS, longest diameter (LDi), and portal vein invasion would affect the response outcome in patients with HCC. In patients with ECOG PS < 2, the ORR and DCR were 52.2% (95% CI = 37.4–67.0%) and 84.8% (95% CI = 74.1–95.4%), respectively, which were significantly higher than those with ECOG PS ≥ 2. Similar superiority was shown in the patients with VAS < 5,

TABLE 2 | Objective response rate (ORR) and disease control rate (DCR) and subgroup analyses.

Response	mRECIST criteria, CR/ORR/DCR		RECIST1.1 criteria, ORR/DCR	
	PLC, n=85	MLC, n=190	PLC, n=85	MLC, n=190
Total, %	63.5/71.8/81.2	49.5/63.7/83.2	32.9/74.1	30.5/70.5
Age	P=0.790	P=0.890	P=0.433	P=0.418
<65, %	62.5/72.9/83.3	48.0/62.7/81.4	33.3/79.2	34.3/73.5
≥65, %	64.9/70.3/78.4	51.1/64.8/85.2	32.4/67.6	26.1/67.0
Gender	P=0.770	P=0.283	P=0.762	P=0.396
Male, %	60.9/69.4/79.7	45.0/63.1/82.9	31.8/72.5	34.2/73.0
Female, %	75.0/81.3/87.5	55.7/64.6/83.5	37.5/81.3	25.3/67.1
ECOG PS	P=0.019	P=0.006	P=0.000	P=0.001
<2, %	71.7/84.8/89.1	48.1/71.4/90.9	52.2/84.8	44.2/83.1
≥2, %	53.8/56.4/71.8	50.4/58.4/77.9)	10.3/61.5	21.2/61.9
VAS	P=0.017	P=0.415	P=0.000	P=0.632
< 5, %	68.6/82.4/88.2	50.6/64.6/84.3	49.0/86.3	30.9/71.3
≥ 5, %	55.9/55.9/70.6	33.3/50.0/66.7	8.8/55.9	25.0/58.3
Lesions number	P=0.766	P=0.900	P=0.079	0.385
Single, %	68.8/81.3/87.5	48.3/62.1/86.2	56.3/87.5	41.4/75.9
Multiple, %	62.3/69.6/79.7	49.7/64.0/82.6	27.5/71.0	28.6/69.6
LDi[&]	P=0.003	P=0.010	P=0.000	P=0.010
< 5 cm, %	74.5/84.3/94.1	56.3/75.9/89.7	43.1/90.2	41.4/77.0
≥ 5 cm, %	47.1/52.9/61.8	43.7/53.4/77.7	17.6/50.5	21.4/65.0
Portal vein invasion	P=0.001	P=0.000	P=0.003	P=0.007
Yes, %	45.5/51.5/60.6	29.5/47.7/56.8	31.7/57.5	24.5/66.9
No, %	75.0/84.6/94.3	55.5/68.5/91.1	36.3/81.2	40.5/75.7
Tumor location	P=0.056	P=0.388	P=0.093	P=0.120
Right lobe, %	57.1/71.4/71.4	35.7/57.2/78.6	33.2/69.8	27.9/66.7
Left lobe, %	72.2/94.4/100.0	62.5/83.3/95.8	45.9/86.5	38.6/74.9
Both, %	61.6/65.0/76.7	48.6/61.2/81.6	34.8/72.0	29.6/64.2
Stage of PLC	P=0.270	NA	P=0.189	NA
Stage III, %	70.4/77.8/87.0		38.9/79.6	
Stage IV, %	51.6/61.3/71.0		22.6/64.5	
Intrahepatic metastasis status	P=0.881	NA	P=0.844	NA
Yes, %	63.2/73.7/78.9		36.8/78.9	
No, %	63.6/71.2/81.8		31.8/72.7	
Extrahepatic metastases status	P=0.574	P=0.001	P=0.424	P=0.001
Yes, %	59.1/68.2/72.7	42.9/47.1/88.3	27.3/63.6	14.3/67.1
No, %	65.1/73.0/84.1	53.3/73.3/74.3	34.9/77.8	40.0/72.5
Liver metastases present at initial diagnosis	NA	P=0.340	NA	P=0.370
Synchronous, %		51.7/62.1/81.0		25.8/62.1
Metachronous(< 1 year), %		52.5/71.3/85.0		36.3/75.0
Metachronous (≥ 1 year), %		42.3/53.8/82.7		26.9/73.1
Primary tumor site for MLC	NA	P=0.013	NA	P=0.008
Colon, %		58.1/74.4/90.7		39.5/83.7
Pancreas, %		42.9/50.0/73.8		9.5/52.4
Gastric, %		34.5/55.2/82.8		41.4/79.3
Rectum, %		47.1/64.7/95.1		35.3/88.2
Breast, %		70.6/.76.5/82.4		23.5/52.9
Gallbladder, %		70.0/70.0/90.0		10.0/60.0
Others[†], %		43.8/65.6/78.1		43.8/71.9
Histories of disease	P=0.593	P=0.477	P=0.794	P=0.652
Hepatitis B, %	69.2/76.9/84.6	71.4/85.7/85.7	35.9/82.1	28.6/85.7
Liver cirrhosis, %	68.4/78.9/84.2	100/100/100	31.6/78.9	31.6/78.9
Hypertension, %	82.4/82.4/88.2	44.8/69.0/86.2	29.4/70.6	37.9/72.4
Diabetes Mellitus, %	70.0/80.0/90.0	58.8/70.6/88.2	40.0/80.0	23.5/64.7
Prior therapies for liver cancer	P=0.236	P=0.097	P=0.519	P=0.944
Prior ≥one therapies, %	57.1/64.3/64.3	100/100/100	35.7/64.3	33.3/66.7
Naïve, %	64.8/73.2/84.5	47.8/62.5/82.6	34.2/76.1	30.4/70.7
AFP level	P=0.464	P=0.922	P=0.111	P=811
Negative (< 400 µg/L), %	73.7/73.7/84.2	49.1/63.6/83.6	52.6/84.2	29.7/70.3
Positive (≥ 400 µg/L), %	60.1/71.2/80.3	52.0/64.0/80.0	27.3/71.2	36.0/72.0
Time to HIFU[#]	P=0.826	P=0.371	P=0.488	P=0.523
< 3 months, %	62.5/70.0/82.5	55.9/68.8/84.9	27.5/75.0	34.4/72.0
≥ 3 months, %	64.4/73.3/80.0	43.3/58.8/81.4	37.8/73.3	26.9/69.1

(Continued)

TABLE 2 | Continued

Response	mRECIST criteria, CR/ORR/DCR		RECIST1.1 criteria, ORR/DCR	
HIFU sessions	P=0.509	P=0.108	P=0.519	0.042
< 5, %	64.3/64.3/71.4	38.3/53.2/76.6	21.4/64.3	19.1/57.4
≥ 5, %	63.4/73.2/83.1	53.1/67.1/85.3	35.2/76.1	34.3/74.8
Indicated for RFA	P=0.443	P=0.340	P=0.279	P=0.197
Yes, %	70.0/77.5/87.5	53.1/70.4/87.7	35.1/76.0	33.2/73.9
No, %	57.7/68.9/75.5	46.8/58.7/79.8	30.5/65.9	27.8/67.4

All the p-values were from chi-square tests based on the number of patients who achieved CR, PR, SD, and PD in each subgroup.

&LDis for the patients with multiple lesions were the sum of the longest diameter of all these lesions.

#Time to HIFU ablation from the diagnosis of PLC or MLC.

†Others included lung cancer(n=8), esophagus cancer (n=5), renal cancer (n=3), nasopharynx cancer (n=3), melanoma (n=3), cervical cancer (n=2), bladder cancer (n=2), ovarian cancer (n=1), prostatic cancer (n=1), skin cancer (n=1), unknown (n=3).

AFP, alpha-fetoprotein; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HIFU, High-Intensity Focused Ultrasound; LDi, longest diameter; ORR, objective response rate; PLC, primary liver cancer; PD, Progressive Disease; MLC, metastatic liver cancer; PR, partial response; RECIST, response evaluation criteria in solid tumors; RFA, radiofrequency ablation; SD, stable disease; VAS, visual analogue scale.
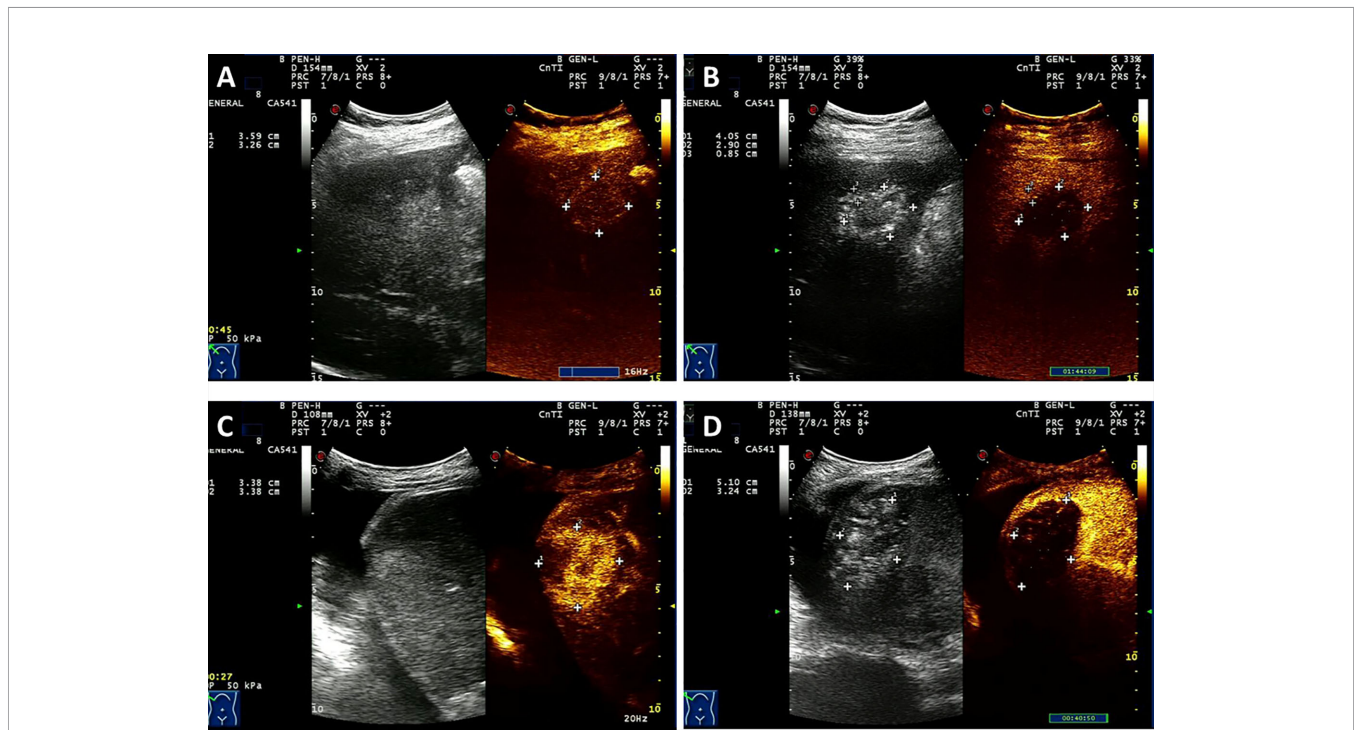

FIGURE 2 | Contrast-enhanced ultrasound (CEUS) of one patient with HCC **(A, B)** and a case with liver metastases from rectal cancer **(C, D)** who was treated with HIFU. A patient was newly diagnosed with stage III HCC by puncture biopsy with AFP level > 1000 U/ml and a previous history of hepatitis B. The patient was treated with HIFU without other therapies. **(A)**. Before HIFU ablation, CEUS depicts the enhancing lesion with a richness of blood supply. **(B)** After treatment, CEUS reveals a completely ablated lesion that shows criteria intratumoral perfusion defect and lacks contrast enhancement. Another patient underwent Dixon surgery and received postsurgery Xelox chemotherapy for six cycles. Twelve months later, hepatic metastatic carcinoma was detected. **(C)** Before HIFU ablation, CEUS depicts the enhancing lesion with a richness of blood supply. **(D)** After HIFU ablation, a intratumoral perfusion defect was seen with no contrast enhancement which indicates complete ablation.

with LDi < 5 cm, and without portal vein invasion (**Table 2**). In the MCL cohort, cases with hepatic metastasis from colon (ORR = 39.5%, DCR = 83.7%) and rectum (ORR = 35.3%, DCR = 88.2%) experienced better response status. Meanwhile, patients with liver metastasis from pancreas (ORR = 9.5%, DCR = 52.4%) and gallbladder (ORR = 10.0%, DCR = 60.0%) had poor response. In addition, some patient characteristics including ECOG PS ≥ 2, LDi ≥ 5 cm, existence of extrahepatic metastases, existence of portal vein invasion, and HIFU ablation times < 5 would diminish the response rate and control rate.

Duration of Response

One hundred eighty-two cases were responding to HIFU ablation by mRECIST, of which the median DOR was 9.5 months with a 95% CI of 8.8–10.2 months. The median DOR was 10.8 (95% CI = 9.8–12.2) months and 8.5 (95% CI = 6.8–9.5)
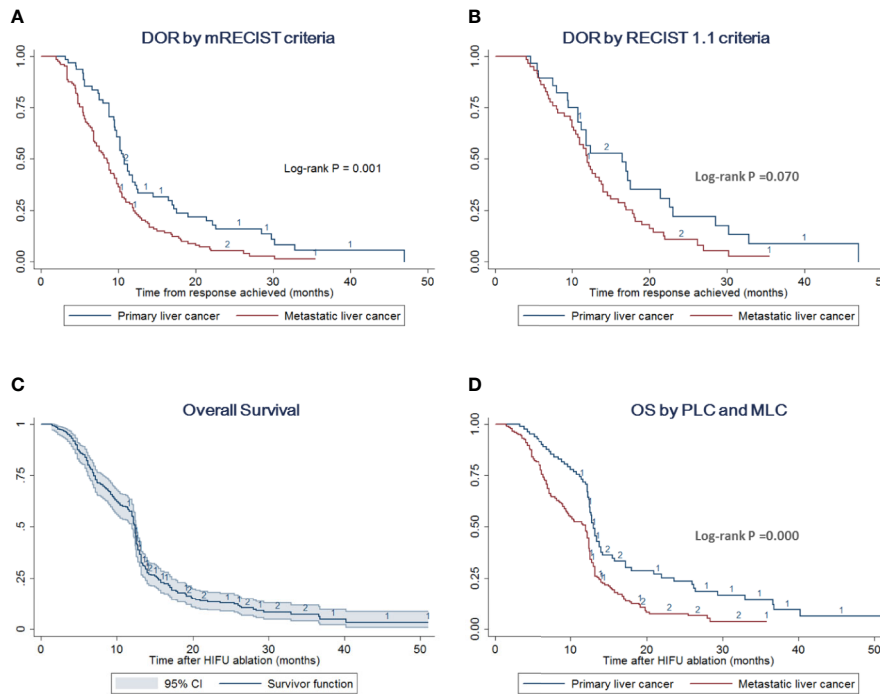
FIGURE 3 | DOR and OS by different liver cancer types. **(A)** DOR stratified analysis by PLC and MLC according to the mRECIST criteria. The log-rank test indicates that patients with PLC prolong the DOR compared with cases with MLC ($p = 0.001$). **(B)** DOR stratified analysis by PLC and MLC according to the RECIST 1.1 criteria. The log-rank test indicates no difference between these two groups ($p = 0.070$) **(C)** OS with 95% CI of the overall cohort including PLC and MLC. **(D)** OS stratified analysis by PLC and MLC. The log-rank test indicates that patients with PLC would improve the survival outcome compared with cases with MLC ($p = 0.000$).

months in 61 responders with HCC and 121 responders with MLC, respectively.

When RECIST 1.1 criteria were used, shown in **Figure 3**, median DOR was calculated to be 12.2 (95% CI = 11.0–14.6) months with a 1-year response rate of 50.98% (95% CI =39.96–60.97%). For 28 responded cases with HCC, DOR was 16.5 (95% CI: 10.8–21.4) months and 1-year response rate was 52.78% (95% CI = 32.84–69.30%). For 58 patients with metastatic liver cancer, in whom a PR was achieved, median DOR was 12.0 months (95% CI = 10.5–13.8). The 1-year response rate was 48.28% (95% CI = 35.00–60.34%). There was no significant difference between these two groups (log-rank P value = 0.07).

AFP and VAS Relief

The relief of AFP levels and VAS scores are presented in **Table 3**. AFP levels were significantly decreased to 361.6 ± 79.3 μg/L in the patients with PLC after HIFU ablation compared with baseline levels of 639.3 ± 106.8 μg/L. An obvious decrease in AFP levels was detected in 43 (50.59%) cases. However, in cases with MLC and the overall cohort, AFP decrease was not significant. Similarly, VAS levels were significantly decreased in the overall cases, especially in the cases with PLC: 38.8% of patients achieved obvious pain relief with VAS reduction of at least 20%, 50%, and 80% in 13 (15.3%), 17 (20.0%), and 3 (3.5%) cases, respectively.

TABLE 3 | Alpha-fetoprotein (AFP) and visual analog scale (VAS) relief.

	PLC, n=85	MLC, n=190	Total, n=275
AFP response			
AFP levels, μg/L; mean ± SE			
Baseline	639.3 ± 106.8	182.7 ± 37.2	323.83 ± 71.3
1 month after HIFU	361.6 ± 79.3*	155.3 ± 44.6	229.13 ± 77.8
Decrease, n (%)			
≥ 20%	27 (31.8%)	7 (3.7%)	34 (12.4%)
≥ 50%	12 (14.1%)	0	12 (4.4%)
≥ 80%	4 (4.7%)	1 (0.5%)	5 (1.8%)
AFP from positive to negative, n (%)	27/66 (40.9%)	3/25 (12.0%)	30/91 (33.0%)
VAS relief			
VAS levels			
Baseline	3.894 ± 1.352	1.942 ± 0.736	2.545 ± 1.143
1 month after HIFU	2.145 ± 0.892*	1.647 ± 0.772	1.800 ± 1.274*
Decrease, n (%)			
≥ 20%	13 (15.3%)	7 (3.7%)	20 (7.3%)
≥ 50%	17 (20.0%)	3 (1.6%)	20 (7.3%)
≥ 80%	3 (3.5%)	0	3 (1.1%)

*$p<0.05$ after HIFU ablation vs. baseline.
AFP, alpha-fetoprotein; HIFU, High-Intensity Focused Ultrasound; PLC, primary liver cancer; MLC, metastatic liver cancer; VAS, visual analogue scale.

OS and Subgroup Analyses

The survival outcomes were recorded in 257 cases out of 275 patients with median follow-up of 18 (range, 2–44) months. The

median OS was estimated to be 12.4 (95% CI = 12–12.6) months with a 1-year survival rate of 55.23% (95% CI = 48.94–61.07%) (**Figure 3**). Separately, patients with PLC had a median OS of 13.0 (95% CI = 12.5–14.0) months with a 1-year survival rate of 70.69% (95% CI = 59.54–79.29%). Meanwhile, the median OS of the MLC group was estimated to be 12.0 (95% CI = 9.5–12.4) months with a 1-year survival rate of 48.00% (95% CI = 40.43–55.16%) (**Figure 3**, **Supplementary Tables 1** and **2**).

In the subgroup analyses of OS for PLC patients, log-rank tests suggested that factors including ECOG PS, VAS, lesion number, LDi, stage, and AFP levels might influence the survival time. Multivariate regression analysis adjusted with the above factors showed that VAS ≥ 5 [(adjusted Hazard ratio (aHR) = 2.784 (95% CI = 1.222–6.250); p=0.015] and LDi ≥ 5 cm

(aHR=4.981 (95% CI = 2.184–11.360); p=0.000) were the independent risk factors for the poor OS outcome (**Figure 4** and **Supplementary Table 1**).

For patients with MLC, independent risk factors were identified as VAS ≥ 5 (aHR= 2.360 (95% CI = 1.182–4.710); p=0.015), LDi ≥ 5 cm (aHR=1.692 (95% CI = 1.178–2.431); p=0.004), existence of extrahepatic metastases (aHR=1.596 (95% CI = 1.109–2.296); p=0.012), and time to HIFU treatment from diagnosis < 3 months (aHR=1.590 (95% CI = 1.106–2.286); p=0.012) (**Figure 4** and **Supplementary Table 2**). These results were adjusted by multiple variables identified in univariate analyses, including gender, ECOG PS, VAS, lesion number, LDi, primary tumor site, extrahepatic metastases status, time to HIFU from diagnosis, and HIFU ablation times.
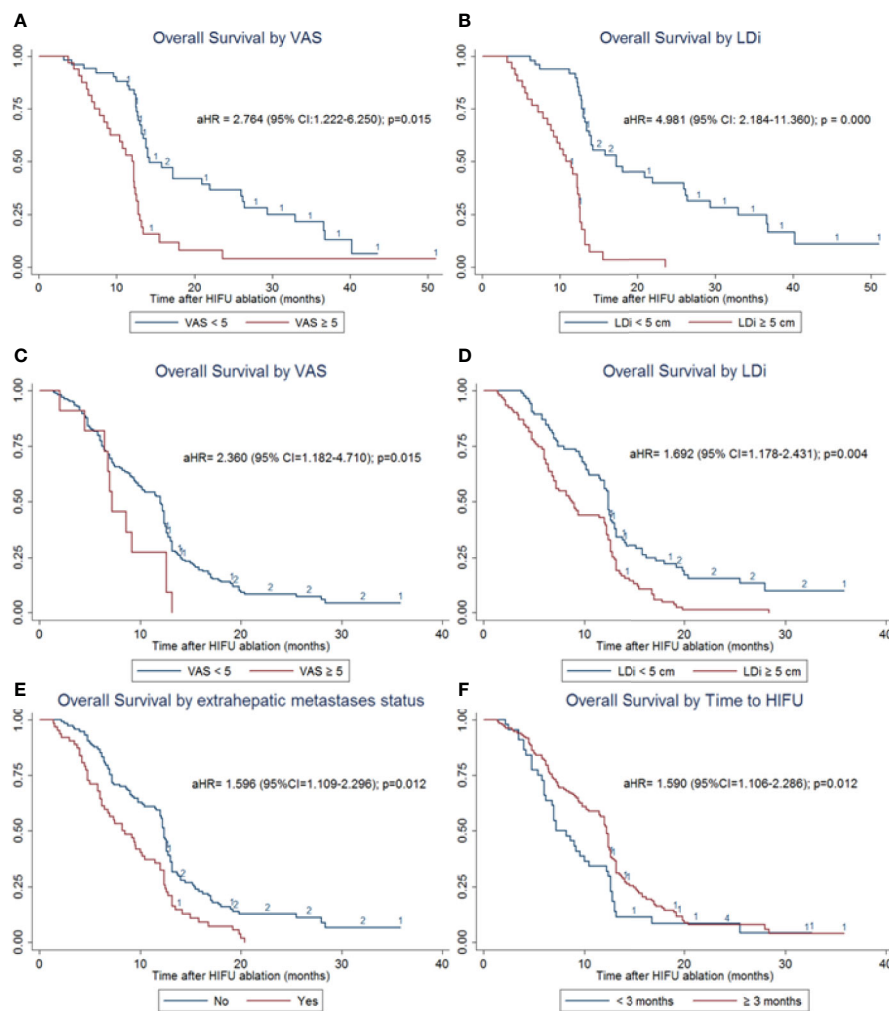

FIGURE 4 | OS subgroup analyses of patients with PLC and MLC. **(A)** OS stratified analysis by VAS in patients with PLC. VAS ≥ 5 significantly increases the risk of death [aHR= 2.784 (95% CI = 1.222–6.250); p = 0.015]. **(B)** OS stratified analysis by LDi in patients with PLC. LDi ≥ 5 cm also significantly increases death risk (aHR = 4.981 (95% CI=2.184–11.360); p = 0.000) **(C)** OS stratified analysis by VAS in patients with MLC. VAS ≥ 5 significantly increases the risk of death (aHR = 2.360 (95% CI=1.182–4.710); p = 0.015). **(D)** OS stratified analysis by LDi in patients with MLC. LDi ≥ 5 cm also significantly increases death risk (aHR = 1.692 (95% CI = 1.178–2.431); p = 0.004). **(E)** OS stratified analysis by extrahepatic metastases status in patients with MLC. Existence of extrahepatic metastases was one of the independent risk factors for poor prognosis (aHR=1.596 (95% CI = 1.109–2.296); p=0.012). **(F)**. OS stratified analysis by the time to HIFU treatment in patients with MLC. Time interval ≥ 3 months was one of the independent risk factors for poor prognosis (aHR=1.590 (95% CI = 1.106–2.286); p = 0.012).

The correlation between OS with RECIST 1.1 or mRECIST was also compared. The response status evaluated by mRECIST criteria was found to be an independent risk factor for OS in cases with both PCL (aHR=1.725 [95% CI = 1.173–2.639], p=0.037) and MCL (aHR=1.350 [95% CI = 1.083–2.350], p=0.014). However, the results based on RECIST 1.1 criteria did not reveal any significant correlation with OS.

HIFU-Related Adverse Events (TEAEs)

Most common TEAEs were body temperature increase (33/275, 12.0%) and abnormal cardiac rhythm (27/275, 9.8%). No skin burns at operation spots occurred. After HIFU ablation, a total of 105 cases (38.2%) reported AEs, of which 51 cases reported more than one complication. Most frequent HIFU-related AEs included fatigue (13.1%), fever (11.3%), abdominal pain (9.8%), rib osteonecrosis injuries (8.7%), diarrhea (5.8%), elevated AST levels (4.0%), elevated ALT levels (3.6%), and rash (2.5%) (**Table 4**). All these complications were mild without the need for symptomatic treatment. Liver abscess and biliary tract obstructions were reported in two patients (0.7%) each. Cases with Liver abscess needed drain placement and antibiotic management. They were discharged from hospital after 17 and 20 days, respectively. Cases with biliary tract obstructions needed stent placement. They were both discharged within a 1-week hospital stay.

DISCUSSION

Patients with HCC are often unresectable at the time of diagnosis and have a poor long-term prognosis, notwithstanding recent advances in TACE (54). Due to its abundant blood supply, the liver is one of the organs most frequently affected by metastatic disease (55). Although percutaneous ablation techniques have been successfully applied for the treatment of hepatic and renal tumors and are now clinically acceptable alternatives to surgery in selected patients (56), similar procedures are not yet considered by current treatment guidelines for PLC or secondary liver cancer (57–60).

Ablation with HIFU is a noninvasive procedure (61, 62) based on the principle that focused ultrasonic beams cause coagulative necrosis of the target tissue. In addition, HIFU might also improve liver function and enhance the immune function of patients with liver cancer, which could benefit the survival of patients (63). In spite of the clinical potential of HIFU ablation, the liver is a particularly challenging organ for this technique due to the combined effect of respiratory-induced liver motion, partial blocking by the rib cage, and high perfusion/flow (64). In general, the application of HIFU in patients with liver cancer, especially in patients with metastatic liver cancer, is still in the exploratory stage.

We prefer to use CEUS, CT, or MRI and not use the echogenic changes as an indicator of the immediate posttreatment response. The echogenic cloud is not as accurate as contrast-enhanced CT or MR for evaluation of the extent of treatment. The echogenic cloud usually overestimates the extent of ablation, and it is difficult to delineate the exact boundaries of the ablated lesion. In addition, with the long ablation time associated with HIFU, the earlier echogenic changes may not be as conspicuous by the end of the procedure, which limits the use of the echogenic cloud for evaluation of the true ablation zone.

As a summary of previous studies (**Table 5**), HIFU has commonly been used for HCC as monotherapy (19–33) or in combination with other therapies, such as TACE (34–42), cryocare knife (65), and SBRT (63, 66). However, very few studies have reported the efficacy of HIFU monotherapy in patients with MLC (20, 24, 43–47) without any HIFU-based combination regimens reported. Among previous studies, high heterogeneity of the response outcome was detected. It might be caused by different response assessment criteria. We found that when using RECIST 1.1, the ORR and CR were quite low. However, ORR and CR significantly increased up to 100% by using mRECIST (**Table 5**). In our clinical practice, ablation therapies, including HIFU applied in liver cancer, often do not induce tumor shrinkage immediately postprocedure, and some even increased in volume. However, the tumors after HIFU have already been necrotic. In this situation, patients would obtain clinical benefits from HIFU and will achieve long-term survival with tumor (48, 67). Therefore, RECIST 1.1 based on the lesion volume seemed to be unsuitable for HIFU response evaluation. In our investigation, we applied both mRECIST and RECIST 1.1 (**Table 2**) criteria for tumor evaluation. Similarly, we detected great differences in remission rates between the two assessment methods. The CR rate, ORR, and DCR were estimated to be 53.8%, 66.2%, and 82.5% by mRECIST. However, when RECIST 1.1 was used, no CR was identified, and ORR and DCR were 31.3% and 71.6%, respectively, which were also significantly lower than the rates by mRECIST (p=0.001). The correlation between OS with RECIST 1.1 or mRECIST were also compared by us. The response status evaluated by mRECIST criteria was found to be an independent risk factor for OS in cases with both PCL and MCL. However, the results based on the RECIST 1.1 criteria did not reveal any significant correlation with OS. To sum up, we prefer mRECIST as the main criterion of efficacy evaluation in the present study, and the following discussion is mainly based on the data from mRECIST.

In consideration of the high heterogeneity between these studies, we failed to pool these results as a meta-analysis. However, we could estimate rough values of CR rate and ORR

TABLE 4 | Most Frequent HIFU-related Adverse Events.

HIFU-related AEs	PLC (n=85)	MLC (n=190)	Total (N=275)
Fatigue	9 (10.6%)	27 (14.2%)	36 (13.1%)
Fever	6 (7.1%)	25 (13.2%)	31 (11.3%)
Abdominal pain	8 (9.4%)	19 (10.0%)	27 (9.8%)
Rib osteonecrotic injures	7 (8.2%)	17 (8.9%)	24 (8.7%)
Diarrhea	6 (7.1%)	10 (5.3%)	16 (5.8%)
Elevated AST levels	3 (3.5%)	8 (4.2%)	11 (4.0%)
Elevated ALT levels	4 (4.7%)	6 (3.2%)	10 (3.6%)
Rash	2 (2.4%)	5 (2.6%)	7 (2.5%)
Liver abscess	0	2 (1.1%)	2 (0.7%)
Biliary tract obstructions	1 (1.2%)	1 (0.5%)	2 (0.7%)
Total	33* (38.8%)	72# (37.9%)	105 (38.2%)

*Thirteen cases with PLC reported more than one AE.
#Thirty-eight patients with MLC reported more than one AE.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HIFU, High-Intensity Focused Ultrasound; MLC, metastatic liver cancer; PLC, primary liver cancer.

TABLE 5 | Summary of previous data on HIFU ablation for primary and secondary liver cancer.

Study	Therapy	Patients	Response	Survival
PLC				
Wu et al. (19**)**	HIFU	55 Large HCC	ORR*: 52 (94.5%) CR: 2 (3.8%) PR: 50 (90.9%)	6-months OS rate: 86.1% 1-year OS rate: 61.5% 18-months OS rate: 35.3%
Zhou et al. (20**)**	HIFU	8	ORR†: 8 (100.0%) CR: 6 (75.0%) PR: 2 (25.0%)	NA
Zhu et al. (21**)**	HIFU	16	NA	1-year OS rate: 100.0% 2-year OS rate: 83.3%
Zhang et al. (22**)**	HIFU	39 (42 lesions) HCC adjacent to major hepatic veins	ORR¶: 42 (100.0%) CR: 21 (50.0%) PR: 21 (50.0%)	1-year OS rate: 75.8% 2-year OS rate: 63.6% 3-year OS rate: 49.8% 4-year OS rate: 31.8% 5-year OS rate: 31.8%
Zhang et al. (23**)**	HIFU	6	CR¶: 6 (100.0%)	NA
Orsi et al. (24**)**	HIFU	6 Small HCC	CR†: 6 (100.0%)	2-year OS rate: 100.0%
Numata et al. (25**)**	HIFU	21	CR#:18 (85.7%)	NA
Ng et al. (26**)**	HIFU	49	CR#: 39 (79.5%)	1-year OS rate: 87.7% 3-year OS rate: 62.4%
Fukuda et al. (27**)**	HIFU	12 Small HCC	CR#: 12 (100.0%)	NA
Zhang et al. (28**)**	HIFU	27 (39 lesions)	CR¶: 28 (71.8%)	NA
Chan et al. (29**)**	HIFU	27	ORR#: 27 (100%) CR: 23 (85.2%) PR: 4(14.8%)	1-year OS rate: 96.3% 2-year OS rate: 81.5% 3-year OS rate: 69.8%
Cheung et al. (30**)**	HIFU	100 Mixed&	CR$: 87%	NA
Cheung et al. (31**)**	HIFU	10 waitlisted for OLT	ORR#: 10 (100%) CR: 9 (90.0%) PR: 1 (10.0%)	NA
Cheung et al. (32**)**	HIFU	26 Recurrent HCC	ORR#: 15 (57.7%) CR: 13 (50%) PR: 2 (7.7%)	1-year OS rate: 84.6% 3-year OS rate: 49.2% 5-year OS rate: 32.3%
Chok et al. (33**)**	HIFU	21 waitlisted for OLT	ORR#: 8 (38.1%) CR: 7 (33.3%) PR: 1 (4.8%)	NA
Ji et al. (48**)**	HIFU	63	ORR#: 49 (77.8%) CR: 20 (31.7%) PR: 29 (46.1%)	1-year OS rate: 87.3% 2-year OS rate: 44.4%
Wu et al. (34**)**	HIFU+TACE	24	ORR*: 21 (87.5%)	MST: 11.3 months 6-month OS rate: 80.4-85.4% 1-year OS rate: 42.9%
Li 2010 (35**)**	HIFU+TACE	44 Larger HCC	ORR¶: 32(72.8%) CR: 12 (27.3%) PR: 20 (45.5%)	1-year OS rate: 72.7% 2-year OS rate: 50.0% 3-year OS rate: 31.8% 5-year OS rate: 11.4%
Jin et al. (36**)**	HIFU+TACE	73	CR#:33 (45.2%)	MST: 12 months 1-year OS rate: 49.1% 2-year OS rate: 18.8% 3-year OS rate: 8.4%
Xu et al. (37**)**	HIFU or HIFU +TACE/PEI	145	ORR¶: 106 (73.1%) CR: 34 (23.4%) PR: 72 (49.7%)	2-year OS rate: 46.5% (Ib) 2-year OS rate: 46.5% (IIa) 2-year OS rate: 46.5% (IIIa)
Wang et al. (38**)**	HIFU+TACE	12	ORR#: 10 (83.3%) CR: 10 (83.3%) PR: 0	MST: 14 months 1-year OS rate: 91.7% 2-year OS rate: 83.3%
Zhai and Wang (65**)**	HIFU+cryocare knife	40 Advanced liver cancer	ORR*: 27 (67.5%) CR: 7 (17.5%) PR: 20(50.0%)	MST: 16.4 months OS rate: 70.0%

(Continued)

TABLE 5 | Continued

Study	Therapy	Patients	Response	Survival
Wang et al. (66)	HIFU+SBRT	76 Massive HCC	ORR#: 56 (73.7%) CR: 40 (52.6%) PR: 16 (21.2%)	1-year OS rate: 33.0% 3-year OS rate: 20.0% 5-year OS rate: 13.0%
Yu et al. (39)	HIFU+TACE	89	CR#: 58 (65.2%)	NA
Ma et al. (63)	HIFU+SBRT	96	NA	6-month OS rate: 35.3% 1-year OS rate: 10.9%
Huang et al. (40)	HIFU+ TACE/SonoVue	52 (73 lesions)	ORR¶: 51 (69.9%) CR: 27 (37.0%) PR: 34 (22.9%)	MST: 30-33 months 6-month OS rate: 100.0% 1-year OS rate: 89.4-95.2% 2-year OS rate: 89.3-89.4%
Luo and Jiang (41)	HIFU+TACE	45	ORR¶: 38 (84.4%) CR: 15 (33.3%) PR: 23 (51.1%)	NA
Zhang et al. (42)	HIFU+TACE	50 Middle-advanced liver cancer	ORR#: 45 (90.0%) CR: 20 (40.0%) PR: 25 (50.0%)	1-year OS rate: 90.0% 2-year OS rate: 80.0% 5-year OS rate: 50.0%
MLC				
Zhou et al. (20)	HIFU	4	ORRⱦ: 4 (100.0%) CR: 0 PR: 4 (100.0%)	NA
Leslie et al. (43)	HIFU	8	ORRⱦ: 4 (50.0%) CR: 3 (37.5%) PR: 1 (12.5%)	NA
Park et al. (44)	HIFU	10 (13 lesions)	ORR¶: 13 (100.0%) CR: 8 (61.5%) PR: 5 (38.5%)	NA
Orsi et al. (24)	HIFU	24	CRⱦ: 22 (91.7%)	1-year OS rate: 88.2% 2-year OS rate: 88.2%
PLC and MLC				
Orgera et al. (45)	HIFU	8 (13 lesions)	CR#: 11 (84.6%)	NA
Leslie et al. (46)	HIFU	29 Primary or metastatic	ORR#: 27 (93%)	NA
Chen et al. (47)	HIFU	187	ORR#: 128 (68.4%) CR: 55 (29.4%) PR: 73 (39.0%)	NA

Response evaluation was according to RECIST 1.1 criteria.
#Response evaluation was according to the modified RECIST criteria.
CR was defined as total tumor necrosis, and PR was defined as patients with a necrosis area larger than 50%; or with the WHO standard.
&HIFU as primary treatment (n=27); as bridging therapy before OLT (n=3); recurrence of HCC after TACE (n=41); HIFU after partial hepatectomy (n=28); HIFU after OLT (n=1).
$The CR rate was 87% for tumor < 3 cm, with unknown number.
†CR was not defined.
CR, complete response; HCC, hepatocellular carcinoma; HIFU, High-intensity focused ultrasound; OLT, orthotopic liver transplantation; ORR, objective response rate; OS, overall survival; TACE, transarterial chemoembolization; PEI, percutaneous ethanol injection; PLC, primary liver cancer; PR, partial response; MLC, metastatic liver cancer; MST, median survival time; NA, not applied; SBRT, Stereotactic Body Radiation Therapy.

for patients with HCC and MLC who were treated with HIFU. The weighted, pooled CR rates and ORRs were 66% and 83% for HCC and 40% and 73% for MLC, respectively. Our results, CR of 63.5% and ORR of 71.8% for HCC patients and 49.5% and 63.7% in the MCL cohort, were consistent with the existing research.

We conducted subgroup analyses of the response outcomes. Patents with ECOG PS <2, LDi < 5 cm might have a better response no matter whether they are in the PLC or MLC cohorts. Furthermore, metastatic lesions from the colon and rectum also seem to have better response, which might be due to the lower degree of malignant of colorectal cancer itself.

In the present observational study, the 1-year survival rate was 70.69% (95% CI = 59.54–79.29%) in patients with HCC and 48.00% (95% CI = 40.43–55.16%) in patients with MLC. Median OS was 13 and 12 months, respectively. As a comparison, previous studies on HIFU monotherapy for cases with HCC have shown a pooled 1-year survival rate of 81.2% (range: 61.5–100.0%), which was roughly equivalent to our outcome. Only one report (24) has described the 1-year survival rate of 88.2% in 24 patients with MLC, which may be of less statistical power. Therefore, our result in MLC patients seemed to be more meaningful clinical data to reflect the impact of HIFU on the survival of MLC patients. In an intragroup comparison of our study, we found that the OS outcome of patients with PLC was superior to that of patients with MLC (**Figure 3**, p = 0.000). We noted that patients with MLC had worse physical status, more lesions, larger diameter, and more extrahepatic metastasis in baseline characteristics. All these may lead to a worse prognosis of MLC.

To further analyze our survival outcome, we conducted subgroup analyses. Multivariate regression analysis showed

that VAS ≥ 5 and LDi ≥ 5 cm were the independent risk factors for the poor OS outcome in patients with PLC (**Figure 4** and **Supplementary Table 1**). For patients with MLC, independent risk factors were identified as VAS ≥ 5, LDi ≥ 5 cm, existence of extrahepatic metastases, and time to HIFU treatment from diagnosis < 3 months (**Figure 4** and **Supplementary Table 2**). These data have not been provided by previous studies. However, it has certain significance for the choice and prognosis of clinical patient screening and prognosis prediction.

In terms of the TEAEs, rare severe adverse reactions were observed during and after HIFU therapy. Some cases reported slightly elevated temperature, which may have been caused by the absorption heat form the necrotic tumor. These symptoms can restore itself without the need of special treatment. Diarrhea was also reported in rare cases, and we believe that it might also be caused by the water sac, which is cool to cause gastrointestinal discomfort. All these complications were not caused by nontarget sonication. Some patients before HIFU treatment felt stressful. However, after preoperative communication by informing the patient with detailed information during and after HIFU treatment, 90% of patients could control their stress in the appropriate range. Earlier research reports high-frequency HIFU-related complications, especially transient pain and superficial skin burns (81% and 39%, respectively) (46). However, our observation did not reveal any evidence of skin burn complication. The difference in HIFU equipment might cause this contrast. The HIFUNIT-9000 device applied in our center adopts a dual focus mode, which facilitates the reduction of energy on the skin during the operation. However, other types of equipment were without this design.

Several limitations should be acknowledged. (1) This is a single-center study, retrospective in nature, which has limited clinical significance. (2) HIFU ablation was conducted using a specific type of HIFU machine (HIFUINT-9000) that is different from the more commonly used integrated transducer design. The efficacy and safety could not be extended to all the HIFU equipment. (3) We did not compare HIFU with standard of care or other thermal ablation techniques, such as RFA and microwave ablation.

In conclusion, our results, which were based on an observational study of the largest sample size to date, further demonstrate the efficacy and safety of HIFU treatment for patients with primary and secondary liver cancer. HIFU might be one optimal therapy for unresectable hepatic tumor. Further well-designed RCTs are needed to evaluate the clinical efficacy of HIFU ablation, especially in combination regimens.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Huadong Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020. 519164/full#supplementary-material

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA: Cancer J Clini* (2019) 69:7–34. doi: 10.3322/caac.21551
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clini* (2018) 68:394–424. doi: 10.3322/caac.21492
3. Mokdad AA, Hester CA, Singal AG, Yopp AC. Management of hepatocellular in the United States. *Chin Clin Oncol* (2017) 6:21. doi: 10.21037/cco.2017.04.04
4. Rich NE, Yopp AC, Singal AG. Medical Management of Hepatocellular Carcinoma. *J Oncol Pract* (2017) 13:356–64. doi: 10.1200/JOP.2017.022996
5. Galle PR, Tovoli F, Foerster F, Worns MA, Cucchetti A, Bondi L. The treatment of intermediate stage tumours beyond TACE: From surgery to systemic therapy. *J Hepatol* (2017) 67:173–83. doi: 10.1016/j.jhep.2017.03.007
6. Pham TA, Gallo AM, Concepcion W, Esquivel CO, Bonham CA. Effect of Liver Transplant on Long-term Disease-Free Survival in Children With Hepatoblastoma and Hepatocellular Cancer. *JAMA Surgery* (2015) 150:1150–8. doi: 10.1001/jamasurg.2015.1847
7. Chok K. Management of recurrent hepatocellular carcinoma after liver transplant. *World J Hepatol* (2015) 7:1142–8. doi: 10.4254/wjh.v7.i8.1142
8. Sleeman J, Steeg PS. Cancer metastasis as a therapeutic target. *Eur J Cancer* (2010) 46:1177–80. doi: 10.1016/j.ejca.2010.02.039
9. Steeg PS. Targeting metastasis. *Nat Rev Cancer* (2016) 16:201–18. doi: 10.1038/nrc.2016.25
10. Namasivayam S, Martin DR, Saini S. Imaging of liver metastases: MRI. *Cancer Imaging Off Publ Int Cancer Imaging Society* (2007) 7:2–9. doi: 10.1102/1470-7330.2007.0002
11. Swaid F, Downs D, Rosemurgy AS. A practical approach to liver metastasis from unknown primary cancer: What surgeons need to know. *Cancer Genet* (2016) 209:559–66. doi: 10.1016/j.cancergen.2016.08.004

12. Hijazi H, Campeau MP, Roberge D, Donath D, Lapointe R, Vandenbroucke-Menu F, et al. Stereotactic Body Radiotherapy for Inoperable Liver Tumors: Results of a Single Institutional Experience. *Cureus* (2016) 8:e935. doi: 10.7759/cureus.935

13. de Baere T, Tselikas L, Yevich S, Boige V, Deschamps F, Ducreux M, et al. The role of image-guided therapy in the management of colorectal cancer metastatic disease. *Eur J Cancer* (2017) 75:231–42. doi: 10.1016/j.ejca.2017.01.010

14. Kennedy AS. Radiation oncology approaches in liver malignancies. *Am Soc Clin Oncol Educ Book* (2014) 34:Meeting e150-155. doi: 10.14694/EdBook_AM.2014.34.e150

15. Dupre A, Melodelima D, Perol D, Chen Y, Vincenot J, Chapelon JY, et al. Evaluation of the Feasibility, Safety, and Accuracy of an Intraoperative High-intensity Focused Ultrasound Device for Treating Liver Metastases. *J Visualized Experiments JoVE* (2019) 143:e57964. doi: 10.3791/57964

16. Li D, Kang J, Golas BJ, Yeung VW, Madoff DC. Minimally invasive local therapies for liver cancer. *Cancer Biol Med* (2014) 11:217–36. doi: 10.7497/j.issn.2095-3941.2014.04.001

17. Orsi F, Arnone P, Chen W, Zhang L. High intensity focused ultrasound ablation: a new therapeutic option for solid tumors. *J Cancer Res Ther* (2010) 6:414–20. doi: 10.4103/0973-1482.77064

18. Diana M, Schiraldi L, Liu YY, Memeo R, Mutter D, Pessaux P, et al. High intensity focused ultrasound (HIFU) applied to hepato-bilio-pancreatic and the digestive system-current state of the art and future perspectives. *Hepatobiliary Surg Nutr* (2016) 5:329–44. doi: 10.21037/hbsn.2015.11.03

19. Wu F, Wang ZB, Chen WZ, Zhu H, Bai J, Zou JZ, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. *Ann Surg Oncol* (2004) 11:1061–9. doi: 10.1245/ASO.2004.02.026

20. Zhou Q, Zhu XQ, Zhang J, Xu ZL, Lu P, Wu F. Changes in circulating immunosuppressive cytokine levels of cancer patients after high intensity focused ultrasound treatment. *Ultrasound Med Biol* (2008) 34:81–7. doi: 10.1016/j.ultrasmedbio.2007.07.013

21. Zhu H, Zhou K, Zhang L, Jin C, Peng S, Yang W, et al. High intensity focused ultrasound (HIFU) therapy for local treatment of hepatocellular carcinoma: role of partial rib resection. *Eur J Radiol* (2009) 72:160–6. doi: 10.1016/j.ejrad.2008.07.003

22. Zhang L, Zhu H, Jin C, Zhou K, Li K, Su H, et al. High-intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins. *Eur Radiol* (2009) 19:437–45. doi: 10.1007/s00330-008-1137-0

23. Zhang L, Fan WJ, Huang JH, Li CX, Zhao M, Wang LG, et al. Comprehensive sequential interventional therapy for hepatocellular carcinoma. *Chin Med J* (2009) 122:2292–8. doi: 10.3760/cma.j.issn.0366-6999.2009.19.019

24. Orsi F, Zhang L, Arnone P, Orgera G, Bonomo G, Vigna PD, et al. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. *AJR Am J Roentgenol* (2010), 195:W245–252. doi: 10.2214/AJR.09.3321

25. Numata K, Fukuda H, Ohto M, Itou R, Nozaki A, Kondou M, et al. Evaluation of the therapeutic efficacy of high-intensity focused ultrasound ablation of hepatocellular carcinoma by three-dimensional sonography with a perflubutane-based contrast agent. *Eur J Radiol* (2010) 75:e67–75. doi: 10.1016/j.ejrad.2009.11.022

26. Ng KK, Poon RT, Chan SC, Chok KS, Cheung TT, Tung H, et al. High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. *Ann Surgery* (2011) 253:981–7. doi: 10.1097/SLA.0b013e3182128a8b

27. Fukuda H, Ito R, Ohto M, Sakamoto A, Karasawa E, Yamaguchi T, et al. Treatment of small hepatocellular carcinomas with US-guided high-intensity focused ultrasound. *Ultrasound Med Biol* (2011) 37:1222–9. doi: 10.1016/j.ultrasmedbio.2011.04.020

28. Zhang Y, Zhao J, Guo D, Zhong W, Ran L. Evaluation of short-term response of high intensity focused ultrasound ablation for primary hepatic carcinoma: utility of contrast-enhanced MRI and diffusion-weighted imaging. *Eur J Radiol* (2011) 79:347–52. doi: 10.1016/j.ejrad.2010.06.039

29. Chan AC, Cheung TT, Fan ST, Chok KS, Chan SC, Poon RT, et al. Survival analysis of high-intensity focused ultrasound therapy versus radiofrequency ablation in the treatment of recurrent hepatocellular carcinoma. *Ann Surgery* (2013) 257:686–92. doi: 10.1097/SLA.0b013e3182822c02

30. Cheung TT, Chu FS, Jenkins CR, Tsang DS, Chok KS, Chan AC, et al. Tolerance of high-intensity focused ultrasound ablation in patients with hepatocellular carcinoma. *World J Surgery* (2012) 36:2420–7. doi: 10.1007/s00268-012-1660-7

31. Cheung TT, Fan ST, Chan SC, Chok KS, Chu FS, Jenkins CR, et al. High-intensity focused ultrasound ablation: an effective bridging therapy for hepatocellular carcinoma patients. *World J Gastroenterol* (2013) 19:3083–9. doi: 10.3748/wjg.v19.i20.3083

32. Cheung TT, Poon RT, Jenkins CR, Chu FS, Chok KS, Chan AC, et al. Survival analysis of high-intensity focused ultrasound therapy vs. transarterial chemoembolization for unresectable hepatocellular carcinomas. *Liver Int Off J Int Assoc Study Liver* (2014) 34:e136–143. doi: 10.1111/liv.12474

33. Chok KS, heung TT, Lo RC, Chu FS, Tsang SH, Chan AC, et al. Pilot study of high-intensity focused ultrasound ablation as a bridging therapy for hepatocellular carcinoma patients wait-listed for liver transplantation. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Society* (2014) 20:912–21. doi: 10.1002/lt.23892

34. Wu F, Wang ZB, Chen WZ, Zou JZ, Bai J, Zhu H, et al. Advanced hepatocellular carcinoma: treatment with high-intensity focused ultrasound ablation combined with transcatheter arterial embolization. *Radiology* (2005) 235:659–67. doi: 10.1148/radiol.2352030916

35. Li C, Zhang W, Zhang R, Zhang L, Wu P, Zhang F. Therapeutic effects and prognostic factors in high-intensity focused ultrasound combined with chemoembolisation for larger hepatocellular carcinoma. *Eur J Cancer* (2010) 46:2513–21. doi: 10.1016/j.ejca.2010.06.015

36. Jin C, Zhu H, Wang Z, Wu F, Chen W, Li K, et al. High-intensity focused ultrasound combined with transarterial chemoembolization for unresectable hepatocellular carcinoma: long-term follow-up and clinical analysis. *Eur J Radiol* (2011) 80:662–9. doi: 10.1016/j.ejrad.2010.08.042

37. Xu G, Luo G, He L, Li J, Shan H, Zhang R, et al. Follow-up of high-intensity focused ultrasound treatment for patients with hepatocellular carcinoma. *Ultrasound Med Biol* (2011) 37:1993–9. doi: 10.1016/j.ultrasmedbio.2011.08.011

38. Wang S, Yang C, Zhang J, Kong XR, Zhu H, Wu F, et al. First experience of high-intensity focused ultrasound combined with transcatheter arterial embolization as local control for hepatoblastoma. *Hepatology* (2014) 59:170–7. doi: 10.1002/hep.26595

39. Yu JY, Zhang HP, Tang ZY, Zhou J, He XJ, Liu YY, et al. Value of texture analysis based on enhanced MRI for predicting an early therapeutic response to transcatheter arterial chemoembolisation combined with high-intensity focused ultrasound treatment in hepatocellular carcinoma. *Clin Radiol* (2018) 73:758 e759–758 e718. doi: 10.1016/j.crad.2018.04.013

40. Huang L, Zhou K, Zhang J, Ma Y, Yang W, Ran L, et al. Efficacy and safety of high-intensity focused ultrasound ablation for hepatocellular carcinoma by changing the acoustic environment: microbubble contrast agent (SonoVue) and transcatheter arterial chemoembolization. *Int J hyperthermia Off J Eur Soc Hyperthermic Oncol North Am Hyperthermia Group* (2019) 36:244–52. doi: 10.1080/02656736.2018.1558290

41. Luo Y, Jiang Y. Comparison of Efficiency of TACE plus HIFU and TACE alone on Patients with Primary Liver Cancer. *J Coll Physicians Surgeons–Pakistan JCPSP* (2019) 29:414–7. doi: 10.29271/jcpsp.2019.05.414

42. Zhang Q, Bian SQ, Lv W, Kou D, Hu HL, Guo SS, et al. Observation of efficacy of TACE combined with HIFU on patients with middle-advanced liver cancer. *Eur Rev Med Pharmacol Sci* (2019) 23:239–46. doi: 10.26355/eurrev_201908_18653

43. Leslie TA, Kennedy JE, Illing RO, Ter Haar GR, Wu F, Phillips RR, et al. High-intensity focused ultrasound ablation of liver tumours: can radiological assessment predict the histological response? *Br J Radiol* (2008) 81:564–71. doi: 10.1259/bjr/27118953

44. Park MY, Jung SE, Cho SH, Piao XH, Hahn ST, Han JY, et al. Preliminary experience using high intensity focused ultrasound for treating liver metastasis from colon and stomach cancer. *Int J hyperthermia Off J Eur Soc Hyperthermic Oncol North Am Hyperthermia Group* (2009) 25:180–8. doi: 10.1080/02656730802641949

45. Orgera G, Monfardini L, Della Vigna P, Zhang L, Bonomo G, Arnone P, et al. High-intensity focused ultrasound (HIFU) in patients with solid malignancies: evaluation of feasibility, local tumour response and clinical results. *La Radiologia Medica* (2011) 116:734–48. doi: 10.1007/s11547-011-0634-4

46. Leslie T, Ritchie R, Illing R, Ter Haar G, Phillips R, Middleton M, et al. High-intensity focused ultrasound treatment of liver tumours: post-treatment MRI correlates well with intra-operative estimates of treatment volume. *Br J Radiol* (2012) 85:1363–70. doi: 10.1259/bjr/56737365

47. Chen L, Wang K, Chen Z, Meng Z, Chen H, Gao H, et al. High intensity focused ultrasound ablation for patients with inoperable liver cancer. *Hepato Gastroenterol* (2015) 62:140–3. doi: 10.5754/hge14643

48. Ji YS, Zhang Y, Zhu JQ, Zhu LL, Zhu YF, Hu KM, et al. High intensity focused ultrasound (HIFU) for primary hepatocellular carcinoma: a single center experience. *Int J Clin Exp Med* (2017) 10:15432–8.

49. Bruix J, Sherman MD. American Association for the Study of Liver. Management of hepatocellular carcinoma: an update. *Hepatology* (2011) 53:1020–2. doi: 10.1002/hep.24199

50. Zhao H, Therasse P, Yang G, Wang D, Yu X, Zhang Y, Zhu J, et al. Concurrent gemcitabine and high-intensity focused ultrasound therapy in patients with locally advanced pancreatic cancer. *Anti-cancer Drugs* (2010) 21:447–52. doi: 10.1097/CAD.0b013e32833641a7

51. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Institute* (2000) 92:205–16. doi: 10.1093/jnci/92.18.1534

52. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* (2009) 45:228–47. doi: 10.1016/j.ejca.2008.10.026

53. Liu YJ, Zhu GP, Guan XY. Comparison of the NCI-CTCAE version 4.0 and version 3.0 in assessing chemoradiation-induced oral mucositis for locally advanced nasopharyngeal carcinoma. *Oral Oncol* (2012) 48:554–9. doi: 10.1016/j.oraloncology.2012.01.004

54. Tsochatzis E, Meyer T, O'Beirne J, Burroughs AK. Transarterial chemoembolisation is not superior to embolisation alone: the recent European Association for the Study of the Liver (EASL) - European Organisation for Research and Treatment of Cancer (EORTC) guidelines. *Eur J Cancer* (2013) 49:1509–10. doi: 10.1016/j.ejca.2012.11.012

55. Fahlenkamp UL, Engel G, Adams LC, Boker SM, Huynh Anh M, Wagner M, et al. Improved visualisation of hepatic metastases in gadoxetate disodium-enhanced MRI: Potential of contrast-optimised (phase-sensitive) inversion recovery imaging. *PloS One* (2019) 14:e0213408. doi: 10.1371/journal.pone.0213408

56. Ahmed M, Brace CL, Lee FT Jr, Goldberg SN. Principles of and advances in percutaneous ablation. *Radiology* (2011) 258:351–69. doi: 10.1148/radiol.10081634

57. Kudo M, Kitano M, Sakurai T, Nishida N. General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Nationwide Follow-Up Survey and Clinical Practice Guidelines: The Outstanding Achievements of the Liver Cancer Study Group of Japan. *Digest Dis* (2015) 33:765–70. doi: 10.1159/000439101

58. China Association of Professional Committee of Liver Cancer. Evidence-based practice guidelines for standardized pathological diagnosis of primary liver cancer in China: 2015. *Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chin J Hepatol* (2015) 23:321–7. doi: 10.3760/cma.j.issn.1007-3418.2015.05.001

59. Zhou J, Sun HC, Wang Z, Cong WM, Wang JH, Zeng MS, et al. Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2017 Edition). *Liver Cancer* (2018) 7:235–60. doi: 10.1159/000488035

60. Zhu D, Ren L, Xu J. Interpretation of guidelines for the diagnosis and comprehensive treatment of colorectal cancer liver metastases in China(v2013). *Zhonghua wei chang wai ke za zhi = Chin J Gastrointest Surgery* (2014) 17:525–9. doi: 10.3760/cma.j.issn.1671-0274.2014.06.002

61. Zhou YF. High intensity focused ultrasound in clinical tumor ablation. *World J Clin Oncol* (2011) 2:8–27. doi: 10.5306/wjco.v2.i1.8

62. Zhang L, Wang ZB. High-intensity focused ultrasound tumor ablation: review of ten years of clinical experience. *Front Med China* (2010) 4:294–302. doi: 10.1007/s11684-010-0092-8

63. Ma B, Liu X, Yu Z. The effect of high intensity focused ultrasound on the treatment of liver cancer and patients' immunity. *Cancer Biomarkers Section A Dis Markers* (2019) 24:85–90. doi: 10.3233/CBM-181822

64. Aubry JF, Pauly KB, Moonen C, Haar GT, Ries M, Salomir R, et al. The road to clinical use of high-intensity focused ultrasound for liver cancer: technical and clinical consensus. *J Ther Ultrasound* (2013) 1:13. doi: 10.1186/2050-5736-1-13

65. Zhai YP, Wang Y. Effect of the combination treatment of high-intensity focused ultrasound and cryocare knife in advanced liver cancer. *J B U ON Off J Balkan Union Oncol* (2017) 22:495–9.

66. Wang L, Li L, Wang X, Zhao D, Shan G, Wu X, et al. Comparison of Combination Stereotactic Body Radiotherapy Plus High-Intensity Focused Ultrasound Ablation Versus Stereotactic Body Radiotherapy Alone for Massive Hepatocellular Carcinoma. *Med Sci Monit Int Med J Exp Clin Res* (2018) 24:8298–305. doi: 10.12659/MSM.910735

67. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Institute* (2008) 100:698–711. doi: 10.1093/jnci/djn134