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Imaging Findings Within the First 12 Months of Hepatocellular Carcinoma Treated With Stereotactic Body Radiation Therapy

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Abstract

Purpose—To correlate the imaging findings of treated hepatocellular carcinoma (HCC) after stereotactic body radiation therapy (SBRT) with explant pathology and alpha-fetoprotein (AFP) response.

Methods and Materials—From 2007 to 2015, of 146 patients treated with liver SBRT for Barcelona Clinic Liver Cancer stage A hepatocellular carcinoma, 10 were identified with inclusion criteria and had regular interval follow-up magnetic resonance imaging/triple phase computed tomography and explant pathology or declining AFP values for radiology-pathology response correlation. Reference standards for successful response were >90% necrosis on explant pathology or pretreatment AFP >75 ng/mL normalizing to <10 ng/mL within 1 year after SBRT without other treatment. Subjects were treated with 24 to 50 Gy in 3 to 5 fractions. Multiphasic magnetic resonance imaging or computed tomography performed at 3, 6, 9, and 12 months after SBRT was compared with pretreatment imaging by 2 expert radiologists. Descriptive statistics were calculated.

Results—There were 10 subjects with 10 treated HCCs, classified as 3 Organ Procurement and Transplantation Network (OPTN) 5a, 4 OPTN 5b, and 3 OPTN 5x. All had successfully treated HCCs, according to explant pathology or declining AFP. Four of 10 HCCs had persistent central arterial hyperenhancement 3 to 12 months after SBRT; persistent wash-out was common up to 12 months (9 of 10). Of 10 treated HCCs, 9 exhibited decreased size at 12 months. Liver parenchyma adjacent to the lesion showed early (3–6 months) hyperemia followed by late (6–12 months) capsular retraction and delayed enhancement. No patient had a significant decline in liver function.

Conclusions—In the absence of increasing size, persistent central arterial hyperenhancement and wash-out can occur within the first 12 months after SBRT in successfully treated HCCs and may not represent residual viable tumor. Liver parenchyma adjacent to the treated lesion showed inflammation followed by fibrosis, without significant change in hepatic function. Until a

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radiologic signature of tumor control is determined, freedom from local progression seems to be the best measure of HCC control after SBRT.

Introduction

Approximately 80% of patients with hepatocellular carcinoma (HCC) are not eligible for definitive surgical treatment (1), usually secondary to the severity of their underlying liver disease, other medical comorbidities, or extent of HCC (ie, size, location, number, vascular invasion, or extrahepatic involvement) (1, 2). For these patients, locoregional treatment options include thermal ablation (eg, microwave, radiofrequency), transarterial chemoembolization (TACE), Y-90 radioembolization, stereotactic body radiation therapy (SBRT), and combination therapies (3–6).

The usual criteria for measuring residual disease after ablation or TACE (ie, size of residual arterially hyper-enhancing components; European Association for the Study of Liver Diseases [EASL] criteria [7] and modified RECIST [mRECIST] criteria [8]) may not apply to HCCs treated with radiation (9, 10) and could lead to inaccurate interpretation of response or inappropriate treatment allocation. We report preliminary data reviewing imaging findings on a small cohort of patients who underwent SBRT for HCC, in which all treated lesions had explant pathology showing near-complete or complete nonviable tissue or normalization of alpha-fetoprotein (AFP) levels as reference standards.

Methods and Materials

After institutional review board approval, 146 subjects undergoing SBRT for HCC were retrospectively identified, of whom 10 met all inclusion criteria (Table 1). Inclusion criteria were: (*1*) HCC treated with SBRT; (*2*) hepatic transplantation with >90% necrosis of the treated HCC, or pretreatment AFP >75 ng/mL normalizing to <10 ng/mL within 1 year after SBRT in the absence of other treatment; (*3*) multiphasic magnetic resonance imaging (MRI) or computed tomography (CT) performed within 3 months before initiation of SBRT; (*4*) at least 1 multiphasic MRI or CT scan performed within 12 months after completion of SBRT; and (*5*) underlying cirrhosis determined by imaging or biopsy. Exclusion criterion was use of other locoregional therapy (eg, TACE, thermal ablation, Y-90 radio-embolization) within 3 months to the same HCC treated with SBRT. Recurrent disease after prior therapy was allowed as long as the other locoregional therapy was not performed within 3 months of the SBRT, and as long as the imaging findings of the recurrent disease met the Liver Imaging Reporting and Data System (LI-RADS) criteria or Organ Procurement and Transplantation Network (OPTN) imaging criteria (ie, OPTN 5) (11). All pretreatment HCCs were classified as definite HCCs using OPTN imaging criteria (ie, OPTN 5) (11–14). The decision to treat with SBRT was made by a weekly multidisciplinary hepatobiliary tumor board.

Of note, the reason for selecting AFP >75 ng/mL was because all patients who had AFP values that were abnormal before SBRT and that normalized after SBRT had levels above 75 ng/mL. Thus, we used the lowest AFP value of the 4 patients who showed normalized AFP after treatment.

Imaging analysis

All subjects underwent multiphasic contrast-enhanced MRI or CT within 3 months before initiating SBRT and at 3-month intervals after treatment. Retrospective imaging interpretation was performed by 2 board-certified radiologists. Key imaging details evaluated included presence of arterial hyperenhancement, wash-out on portal venous phase images, and capsule appearance. The OPTN and LI-RADS version 2014 definitions for the major features of HCC were used (11–14). In addition, size of the tumor was measured in the greatest axial dimension on the arterial phase of imaging.

All HCCs included in the study were considered to be successfully treated by SBRT using 1 of the following reference standards: (*1*) explant pathology correlation showing >90% nonviable tumor at the treatment site as determined by a hepatobiliary pathologist (n=6); or (*2*) AFP >75 ng/mL normalizing to <5 ng/mL within 1 year after SBRT in the absence of other treatment (n=4). The AFP group did not have pathology correlation.

Data are summarized with descriptive statistics.

Results

Ten subjects met inclusion criteria, 1 woman and 9 men, mean age 61 years (range, 44–77 years). All patients had cirrhosis, median Child-Pugh score of 6 (range, 5–8), and good performance status (Eastern Cooperative Oncology Group 0–1). The SBRT doses ranged from 24 Gy/3 fractions to 50 Gy/5 fractions.

Three treated HCCs were OPTN 5a (ie, 1.0–1.9 cm), 4 OPTN 5b (ie, 2.0–5.0 cm), and 3 OPTN 5x (ie, <5 cm) (Figs. 1 and 2, Table 2). All HCCs had arterial hyperenhancement before treatment. All subjects had >90% tumor necrosis after SBRT or a significant reduction in AFP values (pretreatment AFP >75 ng/mL [80; 121; 372; 25,284 ng/mL] and posttreatment AFP <10 ng/mL [2; 6; <2; <2 ng/mL], respectively).

Six patients received hepatic transplant after SBRT, median time 12 months (range, 3–18 months). All 6 patients had dynamic postcontrast imaging performed 0 to 3 months before transplantation. Four patients had normalization of pretreatment AFP values, all of which were normalized by 3 months after SBRT, with follow-up imaging ranging from 5 to 34 months after SBRT.

Four of 10 (40%) successfully treated HCCs demonstrated persistent central arterial hyperenhancement, which was subjectively and objectively diminished in intensity compared with the degree of pretreatment enhancement (Table 2). All 4 tumors with persistent post-SBRT enhancement would have been classified as stable disease according to mRECIST criteria. Persistent wash-out appearance was seen in 9 of 10 treated HCCs, and 9 of 10 tumors decreased in size by 12 months (Table 2). Capsule appearance resolved in 60% of HCCs.

Discussion

The principal findings of this study are that persistent central arterial hyperenhancement was present in 40%, with persistent wash-out seen in 90% of HCCs successfully treated with SBRT within the first 12 months after therapy. None of the masses increased in size. The pattern of enhancement observed after SBRT is different from that expected after successful thermal ablation or TACE, in which residual arterial hyperenhancement is considered viable neoplasm per EASL criteria (7). Thus, inaccurate interpretation of residual arterial hyperenhancement after SBRT risks errors in treatment allocation.

Persistent arterial hyperenhancement after SBRT may be secondary to a giant cell reaction induced by radiation therapy (15). The loss of arterial phase hyperenhancment over time may be secondary to progressive cell death, from coagulation necrosis and fibrosis induced by the targeted radiation (16). Arterial hyperenhancement early in SBRT has been demonstrated on serial CT imaging and can vary by severity of cirrhosis (17, 18). Our study showed similar trends in CT and MR serial imaging. Collectively, this supports the development of novel imaging criteria for the evaluation of HCC treatment response after SBRT.

In conclusion, despite the small sample size, this study is unique because all patients had pathologic evaluation confirming >90% necrosis or normalization of AFP values after SBRT. Standard response assessment criteria for treated HCC, such as EASL (7) and mRECIST (8), may not accurately characterize successful response within the first 12 months after SBRT.

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Summary

In the absence of increasing size, persistent arterial hyperenhancement with wash-out can occur within the first 12 months after stereotactic body radiation therapy (SBRT) in successfully treated hepatocellular carcinomas (HCCs) and should not be confused with residual tumor. Liver parenchyma adjacent to the treated lesion showed inflammation followed by fibrosis, without significant change in hepatic function. Until a radiologic signature of tumor control is determined, freedom from local progression seems to be the best measure of HCC control after SBRT.

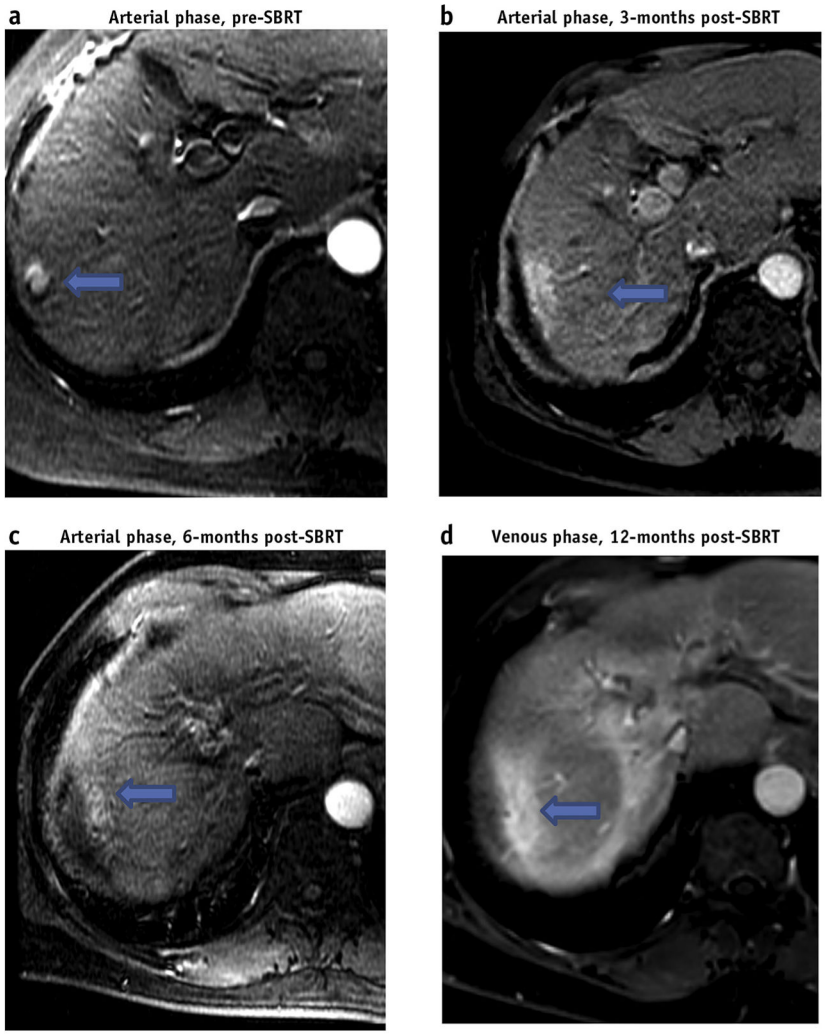
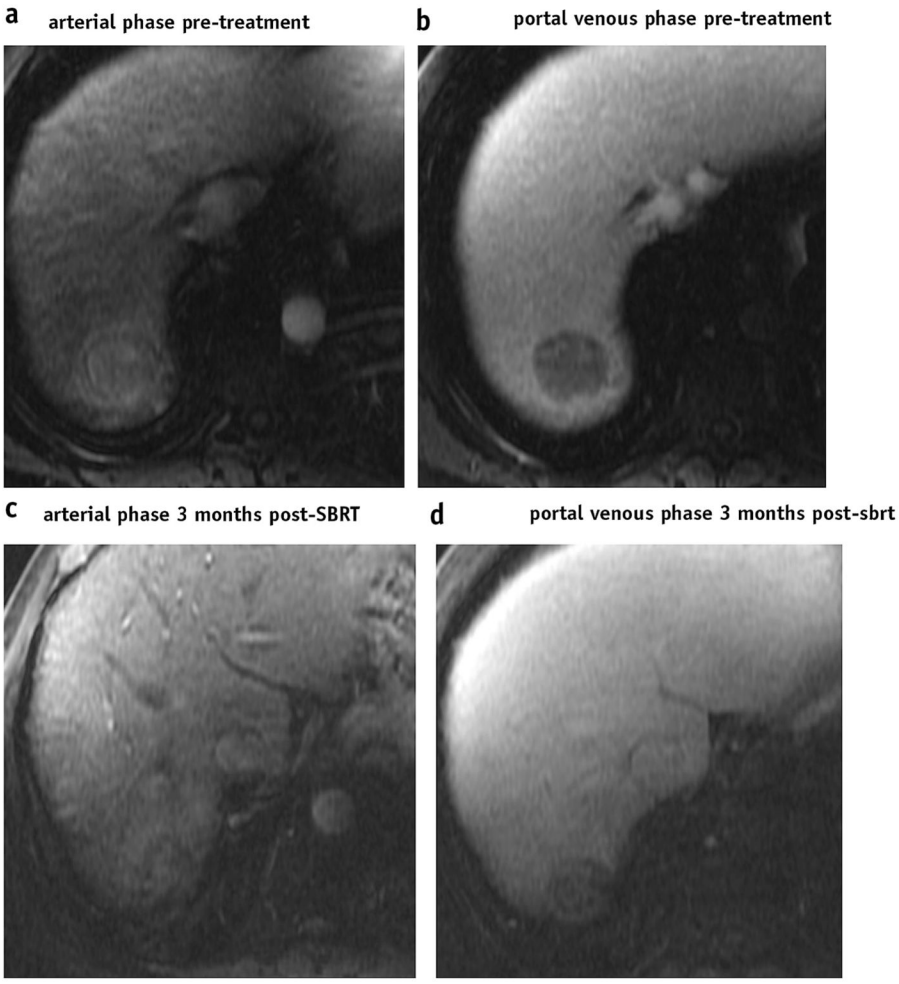


Fig. 1.

A 60-year-old man with hepatitis C–related cirrhosis and a 1.7-cm Organ Procurement and Transplantation Network 5a hepatocellular carcinoma in segment 7 of the liver (subject 2). (a) T1-weighted fat-saturated arterial phase image before stereotactic body radiation therapy (SBRT) shows a hypervascular mass (arrow). (b–d) Arterial phase images at multiple time points after SBRT (b: 3 months; c: 6 months; d: 12 months) are also provided. At 3 months (b) there is regional arterial hyperenhancement obscuring the mass, with no central cavity. At 6 months (c) the arterial hyperenhancement is present but diminished. At 12 months (d), there is volume loss and delayed enhancement in the previously hyperemic parenchyma. Centrally, a small, well-circumscribed, hypoenhancing area is the initial treated hepatocellular carcinoma, now demonstrating loss of enhancement on the arterial phase.



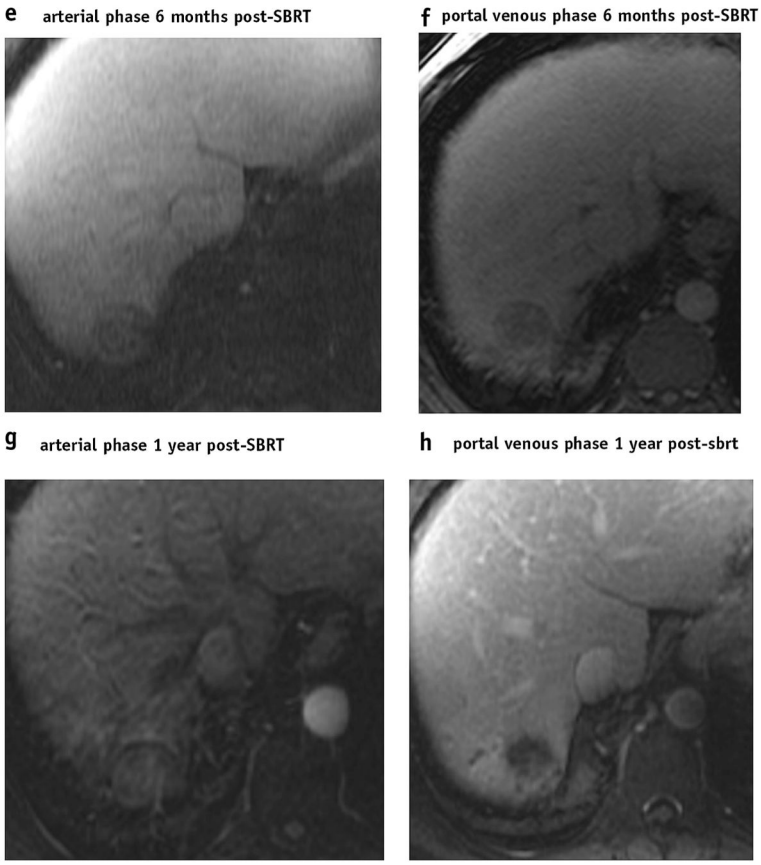


Fig. 2.

A 55-year-old man with hepatitis C–related cirrhosis and a 4.6-cm Organ Procurement and Transplantation Network 5b hepatocellular carcinoma in segment 7 of the liver (subject 4). Imaging is T1-weighted fat-saturated ultrafast spoiled gradient echo imaging in the axial plane before stereotactic body radiation therapy (SBRT) (a, b) and at multiple time points after SBRT (c, d: 3 months; e, f: 6 months; g, h: 12 months). Arterial (a) and portal venous (b) phase images before SBRT show an arterial enhancing lesion with wash-out. Three months after SBRT, arterial (c) and portal venous (d) phase images show persistent arterial enhancement with persistent wash-out; however, the tumor has decreased in size, measuring 3.5 cm. In addition there is surrounding regional arterial phase enhancement of the parenchyma, which normalizes on the portal venous phase. Six months after SBRT, arterial (e) and portal venous (f) phase images show decreasing but persistent central arterial enhancement with persistent wash-out; however, the tumor has decreased in size, measuring 3.4 cm. The surrounding geographic arterial phase hyperenhancement is resolving. One year after SBRT, arterial (g) and portal venous (h) phase images show persistent central arterial enhancement with persistent wash-out; however, the tumor continues to decrease in size, measuring 3.2 cm. There is regional delayed enhancement (h), with progressive off-target parenchymal volume loss.

Table 1

Demographics of HCC SBRT patients

Subject	Age (y)	Sex	ECOG at tx	CP score at tx	Cirrhosis	SBRT dose
1	44	Male	1	6	Yes	30 Gy/3 fx
2	59	Male	0	5	Yes	50 GY/5 fx
3	64	Male	1	6	Yes	36 Gy/3 fx
4	54	Male	0	6	Yes	50 Gy/5 fx
5	58	Male	0	7	Yes	36 Gy/3 fx
6	60	Male	1	8	Yes	34 Gy/3 fx
7	53	Male	0	6	Yes	40 Gy/5 fx
8	77	Male	1	6	Yes	28.2 Gy/5 fx
9	73	Female	0	5	Yes	24 Gy/3 fx
10	72	Male	1	6	Yes	48 Gy/3 fx

Abbreviations: CP = Child-Pugh; ECOG = Eastern Cooperative Oncology Group; fx = fractions; HCC = hepatocellular carcinoma; SBRT = stereotactic body radiation therapy; tx = treatment.

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Table 2

Pre- and dynamic postcontrast imaging appearance of HCC (GTV) successfully treated with SBRT, using explant or AFP response as reference standard

Subject	Size (cm)	% Change	Arterial hyperenhancement	Wash-out	Pseudocapsule	Lipid	Moderate T2w hyperintensity	Impeded diffusion
1 (reference standard: explant shows no viable HCC; baseline AFP 12; AFP before transplant 16); 19 mo from end of SBRT to transplant								
Pre-SBRT	2.4		✓	✓	✓	No	✓	No
3 mo	2.1	−13	No	✓	✓	No	No	No
6 mo	1.9	−21	No	✓	No	No	No	No
12 mo	1.5	−38	No	✓	No	No	No	No
2 (reference standard: explant shows no viable HCC; baseline AFP 6; AFP before transplant 20); 13 mo from end of SBRT to transplant								
Pre-SBRT	1.7		✓	✓	No	✓	No	No
3 mo	0.9	−47	✓	No	No	No	No	No
6 mo	0.8	−53	✓	✓	No	No	No	No
12 mo	0.8	−53	✓	✓	No	No	No	No
3 (reference standard: explant shows >90% necrosis of treated HCC; baseline AFP 5.5; AFP before transplant 4.5); 4 mo from end of SBRT to transplant								
Pre-SBRT	2.0		✓	✓	No	No	No	No
3 mo	1.9	−5	No	No	No	No	No	No
6 mo	-		-	-	-	-	-	-
12 mo	-		-	-	-	-	-	-
4 (reference standard: explant shows >90% necrosis of treated HCC; baseline AFP 3; AFP before transplant 3); 12 mo from end of SBRT to transplant								
Pre-SBRT	4.6		✓	✓		No	✓	✓
3 mo	3.5	−24	No	✓	No	No	No	No
6 mo	3.4	−26	No	✓	No	No	No	No
12 mo	3.2	−30	No	✓	No	No	No	No
5 (reference standard: explant shows >90% necrosis of treated HCC; baseline AFP 2; AFP before transplant 2); 7 mo from end of SBRT to transplant								
Pre-SBRT	1.5		✓	✓	✓	No	No	No
3 mo	1.0	−33	Nondiagnostic	✓	No	No	No	No
6 mo	0.9	−40	✓	✓	No	No	No	No
12 mo	-		-	-	-	-	-	-
6 (reference standard: explant shows no viable HCC; baseline AFP 3; AFP before transplant 2); 3.5 mo from end of SBRT to transplant								
Pre-SBRT	1.5		✓	✓	✓	No	No	No
3 mo	1.5	0	No	✓	✓	No	No	No

Subject	Size (cm)	% Change	Arterial hyperenhancement	Wash-out	Pseudocapsule	Lipid	Moderate T2w hyperintensity	Impeded diffusion
6 mo	-		-	-	-	-	-	-
12 mo	-		-	-	-	-	-	-
7 (reference standard: alfa-fetoprotein response from 25,284 to <2); time to undetectable AFP 9 mo								
Pre-SBRT	6.4		✓	✓	No	No	✓	-
3 mo	3.4	−47	No	✓	No	No	✓	No
6 mo	2.9	−55	No	✓	No	No	No	No
12 mo	2.7	−58	No	✓	No	No	No	No
8 (reference standard: alfa-fetoprotein response from 372 to <2); time to undetectable AFP 3 mo								
Pre-SBRT	7.5		✓	✓	✓	No	Yes	-
3 mo	3.2	−57	No	✓	✓	No	No	No
6 mo	2.0	−73	No	✓	✓	No	No	No
12 mo	-		-	-	-	-	-	-
9 (reference standard: alfa-fetoprotein response from 121 to 6); time to decreased AFP 3 mo								
Pre-SBRT	9.7		✓	✓	✓	No	✓	✓
3 mo	6.4	−34	✓	✓	No	No	No	No
6 mo	-		-	-	-	-	-	-
12 mo	-		-	-	-	-	-	-
10 (reference standard: alfa-fetoprotein response from 80 to 2); time to decreased AFP 6 mo								
Pre-SBRT	3.3		✓	✓	No	-	-	-
3 mo	-		-	-	-	-	-	-
6 mo	2.3	−30	✓	✓	No	-	-	-
12 mo	1.6	−52	No	✓	No	-	-	-

Abbreviations: AFP = alpha-fetoprotein; GTV = gross tumor volume; HCC = hepatocellular carcinoma; SBRT = stereotactic body radiation therapy.

AFP is expressed as ng/mL. Missing data are indicated with (−). “% Change” refers to the percentage change in size compared with the pre-SBRT index examination.