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MR Imaging Evaluation of Hepatocellular Carcinoma Treated with Stereotactic Body Radiation Therapy (SBRT): Long Term Imaging Follow-Up

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Abstract

Purpose: To determine the natural history of imaging findings seen by MRI of hepatocellular carcinoma (HCC) treated with stereotactic body radiation therapy (SBRT). Although arterial hyperenhancement is a key feature of untreated HCC, our clinical experience suggested that tumors which never progressed could still show hyperenhancement. Therefore, we carried out a systematic study to test the hypothesis that persistent arterial phase hyperenhancement (APHE) following SBRT is an expected finding that does not suggest failure of treatment.

Methods: A total of 146 patients undergoing SBRT for HCC between 1/1/2007 and 12/31/2015 were retrospectively screened using an IRB approved prospectively maintained registry. Inclusion criteria were: 1) HCC treated with SBRT, 2) multiphasic MRI 3 months prior to SBRT, 3) up to 1 year of follow-up MRI post-SBRT, and 4) cirrhosis. Exclusion criterion was locoregional therapy 3 months to the liver segment containing the SBRT-treated HCC. Pre- and post-SBRT MR imaging 3 years was analyzed in consensus by independent pairs of subspecialty-trained radiologists to determine the temporal evolution of major features for HCC and imaging findings in off-target parenchyma.

Results: Sixty-two subjects with 67 HCCs (Organ Procurement and Transplantation Network imaging criteria (OPTN) 5a [n=26], OPTN 5b [n=28], OPTN 5x [n=7], Liver Imaging Reporting Data System (LI-RADS) LiRADs-M [n=4], LiRADs-4 [n=2]) were studied. Tumor size either

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decreased (66% [44/67]) or remained unchanged (34% [23/67]) within the first 12 months. Post-SBRT APHE was common (58% [39/67]). When graded by mRECIST criteria at 3-6 months, 25% (17/67) met criteria for complete response (CR) and 75% (50/67) met criteria for stable disease (SD).

Conclusion: SBRT is an effective locoregional treatment option for HCC. Persistent APHE is common and does not necessarily indicate viable neoplasm; thus, standard response assessment such as mRECIST should be used with caution, particularly in the early phases post-SBRT therapy.

Summary:

Persistent arterial phase hyperenhancement is a common finding post stereotactic body radiation for hepatocellular carcinoma and does not indicate viable neoplasm. Standard response assessment by mRECIST should be used with caution. Local progression is better defined by growth of >5 mm or new arterial phase hyperenhancement as post SBRT, most patients developed geographic delayed phase hyperenhancement.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is the 6th most common malignancy worldwide [1]. Approximately 80% of patients diagnosed in the United States with hepatocellular carcinoma (HCC) are not eligible for definitive surgical treatment [2–4]. In patients without a surgical option, non-surgical locoregional treatments may include: thermal ablation (e.g., microwave ablation (MWA), radiofrequency ablation (RFA)), transarterial chemoembolization (TACE), Y-90 radioembolization, and combination therapies [5, 6]. Use of locoregional therapy has been shown to improve disease-free and overall survival in patients who cannot undergo resection [2, 7], and is used as a bridge to transplantation [8] or for down-staging in borderline-eligible patients [9]. Until recently, radiation treatment of HCC has not been a viable option.

Although HCC is a radio-responsive tumor, treatment of HCC with external beam radiation therapy has been limited secondary to off-target liver toxicity [10]. However, the advent of stereotactic body radiotherapy (SBRT) appears to have addressed this issue [11]. SBRT improves upon traditional radiotherapy by precisely delivering a high radiation dose to a tumor while sparing adjacent non-target tissue [11]. Because of these improvements, SBRT has become an additional option in the non-surgical management of hepatic tumors, with a favorable toxicity profile and good local control rates for hepatocellular carcinoma [12–19].

In order to accurately interpret SBRT response on follow-up imaging, it is necessary to understand the evolution of post-treatment changes in the treated HCC and surrounding tissue. Current radiological response assessment criteria used to evaluate treatment efficacy in HCC following locoregional therapy (i.e., EASL criteria [20] and mRECIST [21]) may fail to accurately determine SBRT response because APHE has been shown in small series to persist in effectively treated HCCs [22–24], unlike post-treatment changes seen after other forms of locoregional therapy such as thermal ablation and TACE. This is problematic because inaccurate classification of response could result in treatment misallocation.

Understanding the typical imaging findings of HCC treated with SBRT could mitigate this risk. The purpose of this study was to determine the natural history of the MR imaging appearance of HCC treated with SBRT in the cirrhotic liver.

Materials and Methods

Institutional review board approval was obtained and informed consent waived for this Health Insurance Portability and Accountability Act (HIPAA)-compliant retrospective cohort study.

Subjects

All subjects (n=146) undergoing SBRT for HCC between 1/1/2007 and 12/31/2015 were identified retrospectively using an IRB approved prospectively maintained institutional SBRT registry. The following inclusion criteria were used: 1) hepatocellular carcinoma treated with SBRT, 2) multiphasic MRI performed within 3 months prior to initiation of SBRT, 3) at least one multiphasic MRI performed within 6 months following completion of SBRT, 4) at least 1 year follow-up post-SBRT MRI, and 5) underlying cirrhosis determined by imaging or biopsy. There was one exclusion criterion: use of other locoregional therapy (e.g., TACE, thermal ablation, Y-90 radioembolization) within 3 months to the liver segment containing the SBRT-treated HCC. SBRT of recurrent disease at the treatment zone following prior locoregional therapy to a tumor were included, as long as the prior locoregional therapy was >3 months prior to SBRT. Locoregional therapy to a different segment of the liver was allowed.

Sixty-two subjects with 67 HCC lesions met inclusion and exclusion criteria. Details of the study population are provided in Table 1. All pre-treatment HCCs were classified as definite HCCs by Organ Procurement and Transplantation Network imaging criteria (i.e., OPTN 5) [25] or Liver Imaging Reporting and Data System (LI-RADS) criteria (i.e., LI-RADS 5) [26], or by biopsy.

Imaging

All subjects underwent multiphasic contrast-enhanced MRI within 3 months prior to SBRT. MRI was performed on a 1.5- or 3.0-Tesla magnet using a 16- or 32-channel phased array coil including the following sequences: axial and coronal T2-weighted single-shot fast spin echo, axial T1-weighted dual echo gradient recalled echo (GRE), axial T2-weighted respiratory-triggered fast spin echo (FSE) with fat saturation, axial T1-weighted spoiled GRE with fat saturation pre-contrast and dynamically post-contrast (i.e., arterial [20-30s], venous [60-90s], late dynamic [120-150s]), and axial diffusion-weighted imaging (DWI) with b-values of 0 and 800 s/mm². All subjects undergoing MRI received a weight-based dose of gadobenate dimeglumine (0.2 mmol/kg, maximum dose 20 mL) that was power-injected at 2 mL/sec followed by a 20 mL saline chaser that also was power-injected at 2 mL/sec. Post-contrast imaging was acquired at end-inspiration utilizing either bolus tracking or automated triggering for timing of arterial-phase imaging.

Post-treatment imaging generally was performed with contrast-enhanced MRI at 3-month intervals for the first year after treatment and then variably every 3-6 months thereafter. In some instances, scheduled follow-up imaging was not performed due to clinical factors.

Stereotactic Body Radiation Therapy Procedure

The decision to use SBRT for each subject was made by a weekly multidisciplinary hepatobiliary tumor board that consisted of diagnostic radiologists, interventional radiologists, hepatologists, hepatic surgeons, and radiation oncologists. Generally, SBRT was considered for masses that were difficult to access percutaneously and for subjects with contraindications to other locoregional therapy options. Subjects were treated with a controlled breath-hold technique when possible to minimize motion. For subjects who could not suspend respiration and were free breathing, a 4D-CT was acquired to generate an internal target volume (ITV) and account for tumor excursion. In all subjects, the CT and MRI images were co-registered for delineation of gross tumor volume by the radiation oncologist for treatment planning. Expansion of the gross tumor volume (GTV) to the planning target volume (PTV) for subjects able to breath-hold was 5 mm in the axial dimension and 8 mm in the craniocaudal dimension. Slightly larger margins were used at the discretion of the radiation oncologist depending on the excursion of the tumor in free-breathing subjects. Subjects were treated to 24-60 Gy dose in 3-5 fractions. A range of doses were used and some patients were treated on an adaptive SBRT protocol that permitted a 1-month break between fractions and adaptation of radiation dose based on liver function [27]. Cone beam CT was used to maintain image registration across sessions.

Retrospective Image Review

Imaging interpretation was performed on a picture archiving and communications system (PACS) workstation (McKesson, Richmond BC) by three board-certified abdominal fellowship-trained radiologists with 7 (radiologist A), 3 (radiologist B), and 2 (radiologist C) years' of experience in liver imaging. First, radiologist A reviewed imaging on all 67 HCCs and recorded all primary and secondary outcomes. Next, radiologist B and C each reviewed the dynamic imaging for half of the HCCs (n=33, n=34) unblinded to radiologist A's interpretations to confirm the primary outcomes: lesion size, APHE, washout appearance, and capsule appearance. In cases of disagreement, the disagreement was noted and an independent third radiologist acted as the deciding opinion for final analysis. The goal of the image review was to establish the natural history of imaging findings post-SBRT and not to establish individual radiologist diagnostic accuracy. Therefore, consensus reads were used rather than independent reads. All radiologists were aware of the diagnosis of HCC and that the HCCs were treated with SBRT.

The following details were recorded for each HCC on the pre-treatment and post treatment examinations: location; maximum diameter (measured on T1 pre-contrast or delayed phase sequences and not on the arterial phase sequence, so not to overestimate the tumor size secondary to shunting in the adjacent parenchyma from tumor neovascularity or radiation treatment related changes); relative signal intensity to untreated background parenchyma on T1, T2, and diffusion-weighted imaging; dynamic post-contrast imaging findings including presence of APHE, washout appearance on portal venous and delayed phase images, and

capsule appearance. Persistent APHE of the treated tumor was distinguished from off-target parenchymal arterial enhancement by closely comparing the location and size of the pre-treatment MRI to the post-treatment MRI in order to ensure accurate interpretation of tumoral enhancement versus parenchymal enhancement. The major features for HCC (size, APHE, washout appearance, capsule appearance) were the primary outcomes. The OPTN and LI-RADS v.2014 definitions for the major features of HCC were used [25, 26].

Radiologist A also recorded imaging details for the surrounding off-target hepatic parenchyma on the pre-treatment and post-treatment examinations: relative signal intensity to untreated background parenchyma on T1, T2, and diffusion-weighted imaging; relative signal intensity or attenuation to background parenchyma on pre-contrast and dynamic post-contrast imaging; volume loss; capsular retraction; biliary dilation; bland thrombus; and tumor in vein.

Data Analysis

All analyses were conducted at the lesion level and due to the small number of patients with multiple tumors ($n=4$), outcomes were treated independently. Summary statistics and longitudinal plots were used to summarize the proportion of HCCs that exhibited major qualitative features for HCC (APHE, “washout”, “capsule”) in the pre- and post-treatment examinations. Mean HCC sizes (cm) in the pre- and post-treatment examinations were calculated. Change in size less than 5 mm was considered to be no change in size, as differences of < 5 mm could not be reliably measured. [28, 29] Additionally, measurement differences of 5 mm or less could be erroneous as they may be related to slice thickness. The time-to-loss of arterial hyperenhancement was estimated for patients who had APHE at baseline with the Kaplan-Meier method and associated 95% confidence intervals were calculated. Unblinded reader agreement in calling the major qualitative HCC features was measured with absolute agreement percentages and weighted Kappa (κ) statistics. Analyses were conducted in R version 3.4.2.

Results

Subject and HCC Details

Details of the study population are provided in Table 1. Twenty-six HCCs were OPTN 5a (size 1.0-1.9 cm), 28 were OPTN 5b (size 2.0-5.0 cm), 7 were OPTN 5x (i.e., greater than 5 cm or tumor-in-vein) [Table 1], 4 were biopsy-confirmed LR-M, and 2 were biopsy confirmed LR-4. Twenty-five subjects previously had received 1-6 locoregional therapies to other liver segments greater than 3 months prior to SBRT, which could have been TACE, Y-90, RFA, MWA or resection. 6 patients has SBRT to previously treated lesions, either RFA or TACE, which had local-recurrence >3 months after the initial treatment.

Major Imaging Features of HCC: Temporal Evolution Post-SBRT

Treated HCCs either decreased in size (66% [44/67]) or remained unchanged (34% [23/67]) within the first 12 months [Figure 1–5]. None (0% [0/67]) increased in size in the first 12 months. Two HCCs (3%) increased by 5 mm at 12 ($n=1$) and 14 ($n=1$) months post-SBRT.

On pre-SBRT imaging, 93% (63/67) of HCCs exhibited APHE (61 LiRAD 5 lesions and 2 LiRAD 4 lesions) [Table 2, Figures 1, 2 and 4]. Most (58% [39/67]) had post-SBRT APHE and 16% (11/67) had arterial phase iso-enhancement with respect to the background parenchyma 12 months post-SBRT, indicating that 75% (50/67) of treated HCCs continued to demonstrate solid enhancement post-SBRT [Table 2, Figure 1, 2, 4 and 6a]. Of the HCCs which demonstrated post-SBRT APHE, 37 had APHE pre-treatment and 2 without APHE pre-treatment converted to post-SBRT APHE. Only 25% (17/67) were non-enhancing at the time of first follow-up [Figure 3]. When graded by mRECIST criteria, 25% (17/67) met criteria for complete response (CR) and 75% (50/67) met criteria for stable disease (SD) at the first post-treatment imaging study (3-6 months) [Table 3]. None initially met mRECIST criteria for progressive disease. Over time, the proportion of HCCs exhibiting APHE progressively decreased [Figure 4 and 6].

By 12 months follow-up, 41/67 (61%) of the treated tumors were hypoenhancing on the arterial phase of imaging, which would have been considered CR based on mRECIST criteria. 20/67 (30%) of the treated tumors demonstrated persistent APHE at 12 months, consistent with stable disease (SD) based on mRECIST criteria. There were 6/67 (9%) of the treated tumors at 12 months which demonstrated decreasing intensity and size of enhancement, consisted with partial response (PR) based on mRECIST criteria. (Table 3 and Supplementary figure 1) Of the enhancing patients at baseline, 76% (95% CI: 63-92%), 16% (95% CI: 5-53%) and 8% (95% CI: 1-51%) retained enhancement 1, 2 and 3 years post SBRT. Of the 50 HCCs with persistent solid arterial phase hyper- or iso-enhancement on initial post-SBRT imaging, 30% (n=15) exhibited hyperenhancement, 26% (n=13) exhibited isoenhancement, and 44% (n=22) were non-enhancing at the time of last follow-up (6-36 months).

Pre-SBRT, 91% (61/67) of HCCs had washout appearance and 73% (49/67) had capsule appearance [Table 2]. The proportion with washout appearance (54% [36/67]) and capsule appearance 31% [21/67]) declined by 3-6 months [Table 2]. There was no reliable predictor in regards to which lesions lost wash-out post-SBRT and which did not. Of the 61 HCCs which had APHE and wash-out pre-SBRT, 37 continued to demonstrate APHE and washout at the time of 1st follow-up, 12 demonstrated APHE which persisted on the delayed phase of imaging and 12 converted to non-enhancing post-SBRT, thus no washout on the delayed phase. Time to loss of washout post-treatment in these lesions varied, with 29% (20/67) demonstrating persistent wash-out at 12 months. (Figure 6)

5% (4/67) of the HCCs were hypoenhancing pre-SBRT. 3 months post-SBRT 2 of these lesions remained hypoenhancing through the course of follow-up. 2 lesions converted to post-SBRT APHE at 3 months with decrease in overall size; at 6-month follow-up MRI, both lesions were hypoenhancing. None of these tumors were felt to have detectable tumor progression during the follow-up time period.

Six subjects (9%) had tumor-in-vein on pre-treatment imaging. In all 6 (100%), this became non-enhancing within 12 months.

Ancillary Imaging Features of HCC: Temporal Evolution Post-SBRT

On pre-SBRT imaging, 33% (22/67) of HCCs demonstrated restricted diffusion. Restricted diffusion resolved within 12 months in 82% (18/22) of these 22 masses. The 4 with persistent restricted diffusion did not demonstrate detectable tumor growth during the follow-up time period.

On pre-SBRT imaging, 45% (30/67) of HCCs were hyperintense to background parenchyma on T2w imaging. T2w hyperintensity resolved within 12 months in 82% (18/22) of these 22 masses. The 4 with persistent mild T2w hyperintensity at 12 months were different from the 4 with persistent restricted diffusion at 12 months. and none of these 4 demonstrated detectable tumor growth during the follow-up time period.

Off-Target Hepatic Parenchyma: Temporal Evolution Post-SBRT

The typical enhancement pattern of off-target hepatic parenchyma adjacent to SBRT-treated HCCs was geographic arterial-phase hyperenhancement at 3-6 months (84% [46/55] at 3 months, 85% [56/67] at 6 months) followed by transition to geographic delayed-phase hyperenhancement by 6-12 months (47% [25/57] at 6 months and 83% [43/52] at 12 months) [Figures 1–4].

Capsular retraction (37% [25/67] at 6 months and 78% [52/67] at 12 months) and biliary dilation (7% [5/67] at 6 months and 22% [15/67] at 12 months) peripheral to the SBRT-treated HCCs were common delayed findings.

Progression

Of the 62 patients, none developed extra-hepatic metastasis during the follow-up period. 9 patients developed intra-hepatic progression, none of which were in the SBRT-treatment zone. Eight of the 9 intrahepatic recurrences were located in different segments of the liver than the recent SBRT treated HCC.

The pattern and treatment of these 9 patients is as follows: 2 patients developed new tumor at 3 months; 1 patient developed new tumor at 6 months and underwent RFA; 1 patient developed new tumor at 9 months and underwent TACE; 2 patients developed new tumor at 2 years who underwent TACE; 3 patients developed new tumor at 24 months and were treated with TACE, RFA and MWA, respectively.

4/67 (6%) of the treated tumors were presumed to have detectable tumor growth because of new APHE in non-enhancing treatment cavities (n = 2) and new enlargement of the treatment cavity (n = 2); each manifested >12 months post-SBRT [Figure 4]. Three of these tumors were hypoenhancing within 1 year after SBRT, of which 2 demonstrated new enhancement and 1 had an interval increase in size, thus presumed to be recurrent tumor. One treated tumor had persistent arterial enhancement with continued decrease in size after SBRT, however, presented with increasing size at one year, thus presumed to be recurrent tumor. All 4 presumed local recurrences were re-treated with TACE.

Three (4%) treated HCCs that continued to decrease in size on post-treatment imaging were interpreted during clinical care to demonstrate persistent APHE and thus were considered to contain persistent viable neoplasm.. All 3 were re-treated (n=2 TACE, n=1 ablation).

Unblinded Inter-Reader Consensus

Unblinded inter-reader consensus agreement was moderately high and significantly greater than expected by chance alone (weighted $\kappa=0.74-0.88$) for the major features of HCC on pre- and post-SBRT imaging [Table 3].

Discussion

The key results of our study are that 1) persistent arterial phase hyperenhancement of the treated HCC is a common post-SBRT finding that generally resolves within 12 months, and does not appear to correlate with residual or recurrent tumor, and 2) typical response assessment criteria designed for imaging HCC post-ablation and post-TACE may not be well-suited for evaluating HCC post-SBRT. Although radiotherapy for liver tumors historically has been limited by off-target toxicity (i.e., radiation-induced liver disease), SBRT has addressed this problem and is evolving as a promising treatment option for HCC [10]. Multiple retrospective studies [30–33] have shown high local control rates ranging from 70-90% at 1-2 years; in fact, Takeda et al [34] demonstrated good (72%) 3-year overall survival in previously untreated HCC, while others [35–37] have shown that SBRT can serve as a bridge to transplantation. As the role of SBRT for treatment of HCC in patients with cirrhosis expands, an understanding of the expected post-treatment imaging findings is necessary. We have shown that the typical response assessment criteria designed for imaging HCC post-ablation and post-TACE may not be well-suited for evaluating HCC post-SBRT, particularly when using MRI for evaluating post-treatment response.

We found that 75% (50/67) of SBRT-treated HCCs had persistent solid enhancement at 3-6 months, the majority (78% [39/50]) of which was persistent arterial phase hyperenhancement that gradually disappeared over the first 12 months. Analogous patterns were observed for mass size, washout appearance, and capsule appearance. A recent small (n=10) study from our institution, with a reference standard, observed similar findings [24]. Persistent solid enhancement often was similar in signal intensity to nearby off-target hepatic parenchymal hyperemia and thus obscured. This poses a diagnostic challenge to identify the treated tumor as it blends in with the geographic arterial hyperenhancement in the treatment zone. Accurate understanding of the location and size of the pre-SBRT HCC is critical in order to assess post-SBRT response. This is in contrast to the absent enhancement expected following a successful thermal ablation or TACE. In those settings, residual arterial phase hyperenhancement is correctly interpreted as residual viable neoplasm per EASL and mRECIST criteria [20, 21]. Inaccurate interpretation risks errors in treatment allocation and confounds efforts to validate SBRT efficacy in the context of clinical trials. In our cohort, 3 treated HCCs were likely misinterpreted as harboring residual viable disease during the course of clinical care based on the persistence of solid arterial phase hyperenhancement, despite decrease in size at follow-up imaging, and were re-treated.

Price et al [38] used RECIST and EASL criteria to evaluate response rates of HCC to SBRT and found that 73% [19/26] had a partial or complete response by RECIST and 50% [13/26] exhibited non-enhancement at 12 months. The authors suggested that non-enhancement on imaging may be a more useful indicator of response than change in size, but use of nonenhancement to gauge response is inaccurate in the early post-treatment period. Oldrini et al [39] found a complete response rate of 57% at 3-months by mRECIST criteria that increased to 91% at 12 months. Our complete response rate at 3 months by mRECIST criteria was 25% (stable disease: 75%). In the setting of locoregional therapy for HCC in patients with cirrhosis, misinterpreting successful treatment as stable disease could lead to a high potential for inappropriate re-treatment without knowledge of the typical imaging findings post-SBRT.

Olsen et al has described the histology of two liver metastases treated with SBRT followed by resection [39]. They showed that there was a pauci-cellular collagenized zone centrally, consistent with central liquefaction necrosis. In the zone immediately surrounding this, there was a capillary-rich zone with many lymphocytes and foreign body giant cells. Finally, in the zone surrounding that, there were findings of typical radiation-induced veno-occlusive disease. In the veno-occlusive zone, there was injury to the venule endothelial cells resulting in activation of the clotting cascade, with fibrin deposition and sinusoidal congestion. A recent study by Haddad et al [40] confirmed this pattern of histopathologic findings. Our analysis fits this proposed histologic picture, as HCC treated with SBRT can be persistently hyperenhancing on arterial phase, which could be explained by the giant cell reaction induced by radiation therapy; a finding which would result in arterial phase hyperenhancement. Furthermore, the progressive loss of arterial phase hyperenhancement over time may be secondary to progressive cell death, coagulation necrosis and fibrosis induced by the targeted radiation. [40]

Our study has limitations. Given the retrospective nature of the study, imaging follow-up was not standardized and there was no explant correlation for the treated masses. Presumed local recurrence within 36 months was defined using data from our smaller institutional study [24]. Given the rapid doubling time of HCC [41, 42], years of follow-up is likely a good surrogate for successful treatment. Future prospective work is needed to confirm these findings. Given the retrospective nature of this study, some patients analyzed in the study were treated on an adaptive radiation protocol that allowed a one-month break; we did not observe any differences in post treatment imaging between these groups. Additionally, our study focuses exclusively on treatment response post-SBRT using MRI. We caution extrapolating the data to CT imaging findings without further research in this area. This study focused on arterial enhancement post-SBRT, however, there were patients who had hypovascular tumors which were treated, thus we recommend further dedicated studies to evaluate treatment response after SBRT to hypovascular lesions in order to better understand the natural post-treatment imaging findings seen in this small cohort of patients. In addition, future studies evaluating diffusion restriction is necessary, as diffusion weighted images were not acquired in many of the patients in this cohort. Finally, although wash-out is a major criteria for LiRADS diagnosis of HCC on pre-treatment imaging, the significance of absent or persistent wash-out post-treatment is unclear. Without radiology-pathology

correlation, we caution developing conclusions based on wash-out appearance post-SBRT of HCC until further studies are performed.

In conclusion, SBRT is an effective option for HCC with a low rate of recurrence. Persistent arterial phase hyperenhancement is common, can last for at least 12 months post-SBRT, and does not necessarily indicate viable neoplasm. Therefore, unchanged or shrinking central arterial phase hyperenhancement within a treated HCC within this timeframe should not be interpreted as residual viable neoplasm. Standard response assessment criteria for HCC such as EASL [20] and mRECIST [21] should be used with caution as they may not accurately characterize response soon after SBRT (i.e., before 12 months). Furthermore, imaging findings of increasing size of the treated tumor and/or new or increasing intensity of arterial phase hyperenhancement after SBRT should be evaluated with caution and closely monitored for the potential of tumor growth suggesting recurrent tumor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Persistent APHE for 12 months after SBRT to HCC with progressive decrease in size of the treated tumor.

58-year-old male with hepatitis C-related cirrhosis and a 1.7-cm Organ Procurement and Transplantation Network (OPTN) 5A/LIRADS 5 hepatocellular carcinoma in segment 7 of the liver. Imaging is T1-weighted fat-saturated ultrafast spoiled gradient echo arterial phase (1a) and portal venous phase (1b) image in the axial plane before stereotactic body radiation therapy (SBRT) and at multiple time points after SBRT. At 3 months the lesion has decreased in size, measuring 1.4cm, with persistent arterial phase hyperenhancement (APHE) (1c) and portal venous phase washout appearance and capsule appearance (1d). At 6 months the lesion has decreased in size, measuring 0.8cm, with persistent APHE (1e) and portal venous phase washout appearance and capsule appearance (1f). Additionally, at 6 months, ancillary findings post-SBRT are seen, including: geographic arterial phase parenchymal hyperenhancement (1e) which persists on the portal venous phase (1f), and volume loss of the overlying parenchyma. At 12 months the lesion has decreased in size, measuring 0.7cm, with APHE (1g), and the lesion is no longer seen on the portal venous phase of imaging (1h). Additionally, the arterial phase geographic parenchymal enhancement has resolved, with continued volume loss of the parenchyma.

Figure 2. Persistent APHE for 12 months after SBRT to HCC with progressive decrease in size of the treated tumor.

67-year-old male with alcohol related cirrhosis and a 2.1-cm OPTN 5B/LIRADS 5 hepatocellular carcinoma in segment 2 of the liver. Imaging is T1-weighted fat-saturated ultrafast spoiled gradient echo arterial phase (2a) and portal venous phase (2b) image in the axial plane before SBRT and at multiple time points after SBRT. At 3 months the lesion is relatively stable in size, measuring 2.0cm, with persistent APHE (2c) and portal venous phase washout appearance and capsule appearance (2d). Additionally, at 3 months there is arterial phase greater than portal venous phase geographic parenchymal hyperenhancement with overlying mild capsular retraction, compatible with volume loss. At 6 months the lesion has decreased in size, measuring 1.5cm, with persistent APHE (2e) and portal venous phase washout appearance and capsule appearance (2f). Additionally, there is decreasing geographic arterial phase parenchymal hyperenhancement (2e) which increases on the portal venous phase (2f), and continued capsular retraction/volume loss of the overlying parenchyma.

Figure 3. Post-SBRT with conversion from APHE pre-treatment to arterial phase hypoenhancement immediately after treatment.

63-year-old female with HCV-related cirrhosis and a 1.3-cm OPTN 5A/LIRADS 5 hepatocellular carcinoma in segment 1 of the liver. Imaging includes T1-weighted arterial phase (3a) and portal venous phase (3b) images before SBRT and at multiple time points after SBRT. At 6 months the lesion has decreased in size, measuring 1.0cm, with hypoenhancement on the arterial phase of imaging (3c) and not well seen on PV phase of imaging (3d). Additionally, at 6 months there is arterial greater than portal venous phase geographic parenchymal hyperenhancement, with mild volume loss of the caudate lobe.

Figure 4. Persistent but decreasing APHE post-SBRT for HCC which continues to decrease in size. 18-months post-treatment the tumor increases in size with increasing APHE, suggesting local recurrence.

Patient 4: 54-year-old male with HCV-related cirrhosis presents with a 2.3-cm APHE lesion (4a) which demonstrates washout appearance and capsule appearance on portal venous phase (4b), compatible with OPTN 5B/LIRADS 5 hepatocellular carcinoma in segment 4a of the liver. 3 months post-SBRT, the lesion has decreased in size, measuring 1.9cm, and although still enhancing, it is inconspicuous on arterial phase imaging (4c) secondary to surrounding geographic parenchymal hyperenhancement from radiation; there is washout appearance and capsule appearance on PV phase of imaging (4d). 6 months post-SBRT the lesion continues to decrease in size, measuring 1.5cm, and now is more conspicuous as the geographic arterial phase hyperenhancement begins to resolve (4e). The treated tumor demonstrates persistent APHE (4e) with washout appearance and capsule appearance on portal venous phase (4f). Additionally, at 6 months there is increasing portal venous phase geographic parenchymal hyperenhancement. 15 months post-SBRT the lesion continues to decrease in size, measuring 1.1cm, with mild persistent central APHE (4g) with continued washout appearance and capsule appearance on portal venous phase (4h). Additionally, at 15 months there is portal venous phase geographic parenchymal hyperenhancement with overlying capsular retraction, consistent with volume loss (4h). At 18 months post-SBRT, there is increasing size of the treated HCC, measuring 1.5cm, with increasing solid APHE (4i), and persistent portal venous phase washout appearance and capsule appearance (4j). Increase in size and enhancement is suggestive of local recurrence. In addition, on portal venous phase at 18 months (4j), there is surrounding geographic delayed parenchymal enhancement and volume loss.

Figure 5. Maximum tumor diameter in the first 36 months for HCCs treated with SBRT. Dots are means and lines are 95% confidence intervals.

Figure 6.

A. Time to loss of arterial-phase hyperenhancement in subjects with pre-treatment arterial phase hyperenhancement and B. Time to loss of wash-out (unadjusted Kaplan-Meier plot). Solid line is observed data and dotted lines are 95% confidence intervals.

Table 1.

Study population details. Some subjects had more than one cause of cirrhosis. NASH: non-alcoholic steatohepatitis, Organ Procurement and Transplantation Network (OPTN), Liver Imaging Reporting Data System (LI-RADs).

Characteristic	N (%) or Mean (range)
Subjects	62
Female	19% (12)
Male	81% (50)
Age (years)	64.88 (25-90)
Cirrhosis	100% (62)
Alcohol-related	32% (20)
Hepatitis B	5% (3)
Hepatitis C	58% (36)
NASH	11% (7)
Autoimmune	2% (1)
Other	3% (2)
Prior locoregional therapy to other liver segments	42% (25)
Total HCCs	67
Imaging-Confirmed HCCs	(% of lesions)
OPTN 5 (any)	91% (61)
OPTN 5a	39% (26)
OPTN 5b	42% (28)
OPTN 5X	10% (7)
LI-RADS 5	91% (61)
Biopsy-Confirmed HCCs	(% of lesions)
LR-M	6% (4)
LI-RADS 4 (no biopsy)	3% (2)
Imaging Follow-up (months)	19 (12-36)
SBRT Dose/Fractionation	
Median SBRT physical dose	39.5 Gy (21-60)
Median Total BED	79.2 Gy (35.7-132)
Median SBRT EQD2 dose	66 Gy10 (30-110)
Median Number of Fractions	3 (3-5)
Most Recent Prior Liver Directed Therapy (within 3 months of SBRT)	
None	41
TACE	6
RFA	11
SBRT	3
Resection	5

Table 2:

Imaging appearance of HCCs treated with SBRT on the first imaging time point post-treatment (3 or 6 months depending on clinical care pattern).

Imaging Appearance	Pre-SBRT n=67	First Post-SBRT (3 or 6 months) n=67
Not evaluable	3% (n=2)	3% (n=2)
Arterial Phase		
Hyperenhancement	94% (n=63)	58% (n=39)
Isoenhancement	1% (n=1)	16% (n=11)
Hypoenhancement	3% (n=2)	25% (n=17)
Washout Appearance	91% (n=61)	54% (n=36)
Capsule Appearance	73% (n=49)	31% (n=21)

Table 3:

Modified Response Evaluation Criteria in Solid Tumors (mRECIST) classification of treated tumors up to one year post-SBRT

	mRECIST			
	SD	CR	PR	PD
1 st post-SBRT imaging (3-6 months)	50/67 (75%)	17/67 (25%)	0	0
12-months post-SBRT	20/67 (30%)	41/67 (61%)	6/67 (9%)	0

Table 4.

Unblinded inter-reader consensus for subjective major features of HCC expressed with weighted Kappa (κ) statistics and absolute agreement. Denominators vary by available imaging series.

	Readers A and B		Readers A and C	
	κ	Absolute Agreement	κ	Absolute Agreement
Arterial Phase Hyperenhancement	0.88	88% (105/120)	0.79	89% (127/142)
Capsule Appearance	0.87	95% (55/58)	0.84	92% (59/64)
Washout Appearance	0.77	94% (117/125)	0.74	92% (131/143)
Overall	0.96	91% (277/303)	0.93	91% (317/349)