



Imaging post-stereotactic body radiation therapy responses for hepatocellular carcinoma: typical imaging patterns and pitfalls

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Abstract

Stereotactic body radiation therapy (SBRT) has increased utility in the management of hepatocellular carcinoma (HCC) ranging from local therapy in early-stage HCC not suitable for other focal therapies to end-stage HCC. As the indications for the use of SBRT in HCC expand, diagnostic imaging is being increasingly used to assess response to treatment. The imaging features of tumor response do not parallel those of other focal therapies such as radiofrequency ablation or trans-arterial chemoembolization that immediately devascularize the tumor. The tumor response to SBRT on imaging takes much longer and often shows gradual changes including the reduction of enhancement and size over several months. It is essential to recognize the typical imaging patterns of response, as well as the appearance of focal liver reaction in the non-target liver that can confound image interpretation. The timing of treatment response assessment imaging is fundamental to minimize the potential for false negative response. The purpose of this article is to review the variable post-SBRT imaging features of HCC and adjacent liver parenchyma and discuss the potential pitfalls of imaging evaluation after SBRT for HCC.

Keywords Hepatocellular carcinoma · Stereotactic body radiation therapy · Imaging · Treatment response · CT · MRI

Introduction

The clinical use of radiotherapy of the liver for hepatocellular carcinoma (HCC) was historically limited due to low tolerance of the adjacent (usually diseased) liver parenchyma to high dose radiation [1] and technical limitations in delivering ablative doses to the tumor while limiting radiation-induced liver damage (RILD) [2, 3]. Advanced radiotherapy

technologies, such as stereotactic body radiation therapy (SBRT), have allowed dose escalation to focal lesions [4] and rapid fall off of radiation dose to adjacent tissues with a resulting highly conformal ablative radiation dose to the target lesion [5], and therefore, increased the use of SBRT in the liver.

Tumor cell death after radiation therapy is multifactorial and, over time, the tumor bed is replaced by dense fibrosis with areas of necrosis. The adjacent non-target liver parenchyma undergoes changes of an inflammatory response similar to veno-occlusive disease, with ultimate shrinkage and fibrosis of the irradiated liver, and often associated hypertrophy of the spared liver [6].

As the indications for SBRT to HCC expand, imaging follow-up to assess treatment response is becoming more widely used. The imaging appearance of HCC following SBRT does not parallel the treatment response that occurs following other focal therapies. Response evaluation criteria in solid tumors (RECIST) is based on a change in the size of the tumor [7], but areas of necrosis following SBRT are not considered in RECIST. Modified RECIST (mRECIST) and European Association for the Study of the Liver (EASL) criteria [8] take into account viable tumor within the

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lesion, but have not been validated for use in the post-SBRT response of HCC. More recently, proton beam therapy and carbon ion radiotherapy, given their physical properties that provide dose deposit at the Bragg peak with little or no exit dose, have also emerged as promising radiation treatment modalities to minimize RILD while maintaining high rates of local control [9]. It is not known if treatment response and adjacent focal liver reaction would follow different imaging appearances from post-SBRT treatment change.

In this review, we present the different imaging appearance of HCC treated with SBRT and the appearance of focal liver reaction in the non-target liver and discuss the potential pitfalls in the assessment of treatment response.

SBRT for HCC

In SBRT, tumor kill is maximized and dose to the surrounding organs at risk is minimized by precise and accurate delivery of multiple beams to the target in a limited number high-dose fractions. Liver SBRT is particularly challenging, given that tumors move with respiration and are often irregular in shape, requiring careful treatment planning and motion management during treatment (e.g. breath-hold, abdominal compression) and image guidance before or during each radiation therapy fraction [10].

During the treatment simulation process, both a multiphase contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are utilized to contour the gross tumor volume (GTV) [11]. Primary liver cancer is best seen in the arterial or delayed phase CT, with vascular invasion of HCC best seen in the portal venous phase. Then a planning target volume (PTV) is expanded from the GTV to account for organ motion and residual positioning uncertainty. The final prescription dose is individualized and based on the volume of normal tissues irradiated (correlated with the mean liver dose), as well as the proximity to gastrointestinal luminal organs, such as the stomach, duodenum, small and large bowel, to the target volumes.

Indications for SBRT to HCC

With radiotherapy previously limited to palliation for symptomatic advanced disease, multiple advances in radiation therapy delivery have led to expanding indications in the management of HCC.

The role of SBRT for the treatment of HCC is still not completely defined and will differ based on practices in different centers. Although radiotherapy is not part of the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm, multiple single-arm series and phase II clinical trials have

shown a potential for SBRT to lead to long-term control and survival [12, 13].

Currently, SBRT is used for intermediate or advanced stage HCC with tumor thrombus in the portal vein [1]; intermediate or advanced stage HCC unsuitable or refractory to trans-arterial chemoembolization (TACE); early stage HCC unsuitable for resection, transplantation or local ablation [1, 14, 15]; as a bridging therapy to liver transplantation [1, 14–16]; and for symptomatic end-stage HCC for both the primary tumor and metastases [1]. Furthermore, multiple randomized clinical trials are ongoing in the intermediate and advanced stage setting that will further define the role of SBRT in this treatment population.

Not all patients with HCC are suitable for SBRT. Clinical factors as well as SBRT details and liver dose-volume histogram parameters need to be considered, as baseline Child–Pugh scores and higher liver doses correlate with liver function decline 3 months post-SBRT [17]. Currently, its use is most appropriate in patients with Child–Pugh A cirrhosis. In patients with Child–Pugh B7 score, close clinical surveillance and SBRT dose reduction is recommended due to the higher risk of RILD [18]. The risk of RILD is high in Child–Pugh B and C, and SBRT should be limited to those with Child–Pugh B7 liver function or smaller lesions [18]. The tumor number also limits SBRT use, with current recommendations for use in a limited number of lesions [19], for example up to 5. The location of tumors in the liver is also important to consider when doing radiation planning and dose allocation, with an assessment of whether the lesions are clustered or widely dispersed. Regarding tumor location in the liver, a minimum distance of the target lesion from adjacent hollow viscera of 5 mm is recommended, although in our experience tumors abutting luminal organs can be treated by limiting the delivered dose to the organ tolerance (between 27.5 and 30.0 Gy in 5 fractions). Factors that limit the use of other focal therapies, such as tumor location relative to vessels, the intrahepatic biliary tree or the diaphragmatic surface of the liver, do not prevent the use of SBRT.

Pathological changes of HCC and adjacent liver post SBRT

The mechanism of cell death in SBRT is multifactorial. Coagulation necrosis of the target tissue is often gradual after SBRT and is eventually replaced by fibrosis in cases with successful SBRT [20]. Primary death, however, is by clonogenic death that results in DNA breakdown and cell death at the time of replication. Other types of cell death following SBRT include mitotic catastrophe, apoptosis, senescence, necrosis and autophagy. In the liver parenchyma surrounding the target lesion, there is hyperemia due

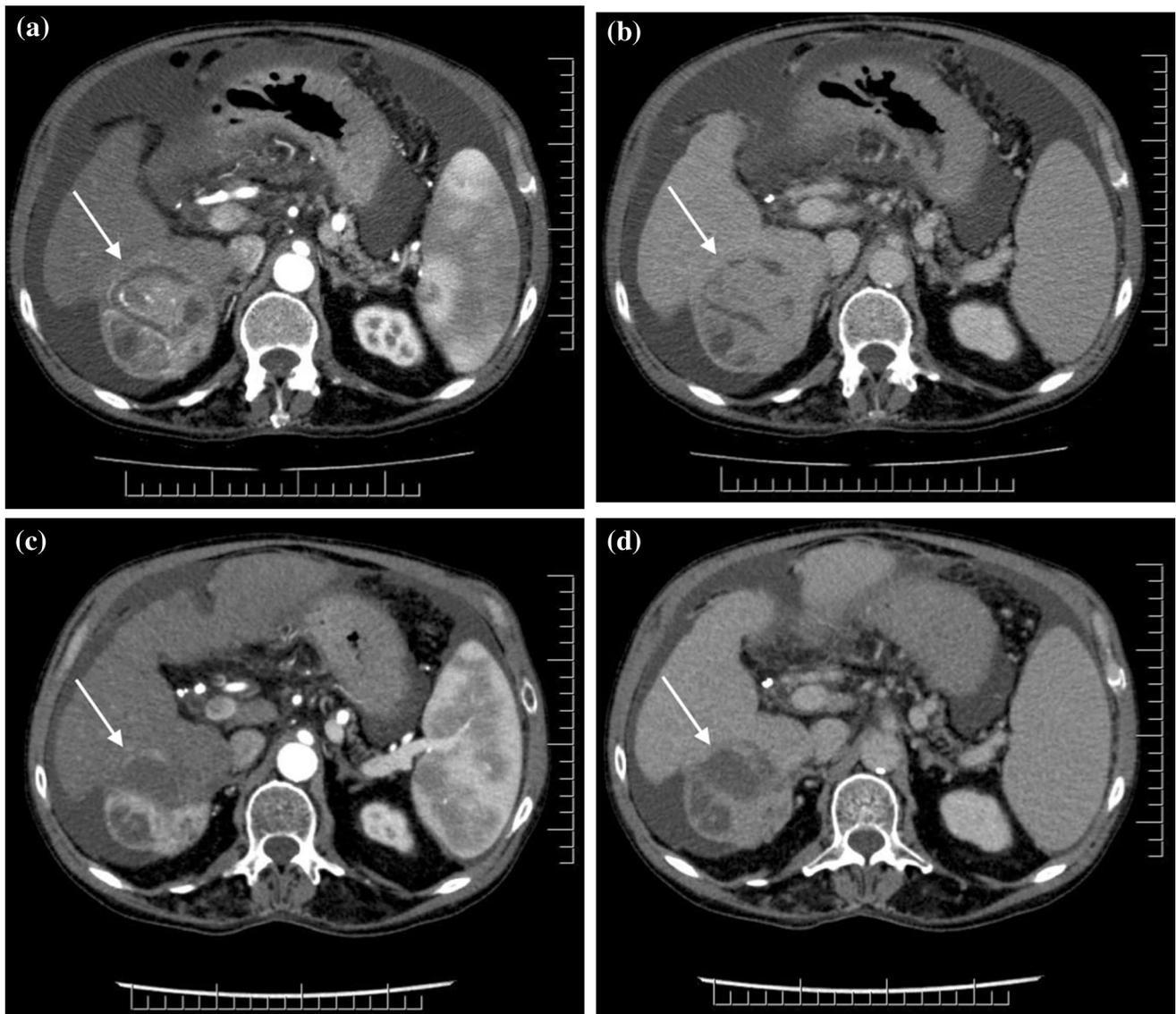


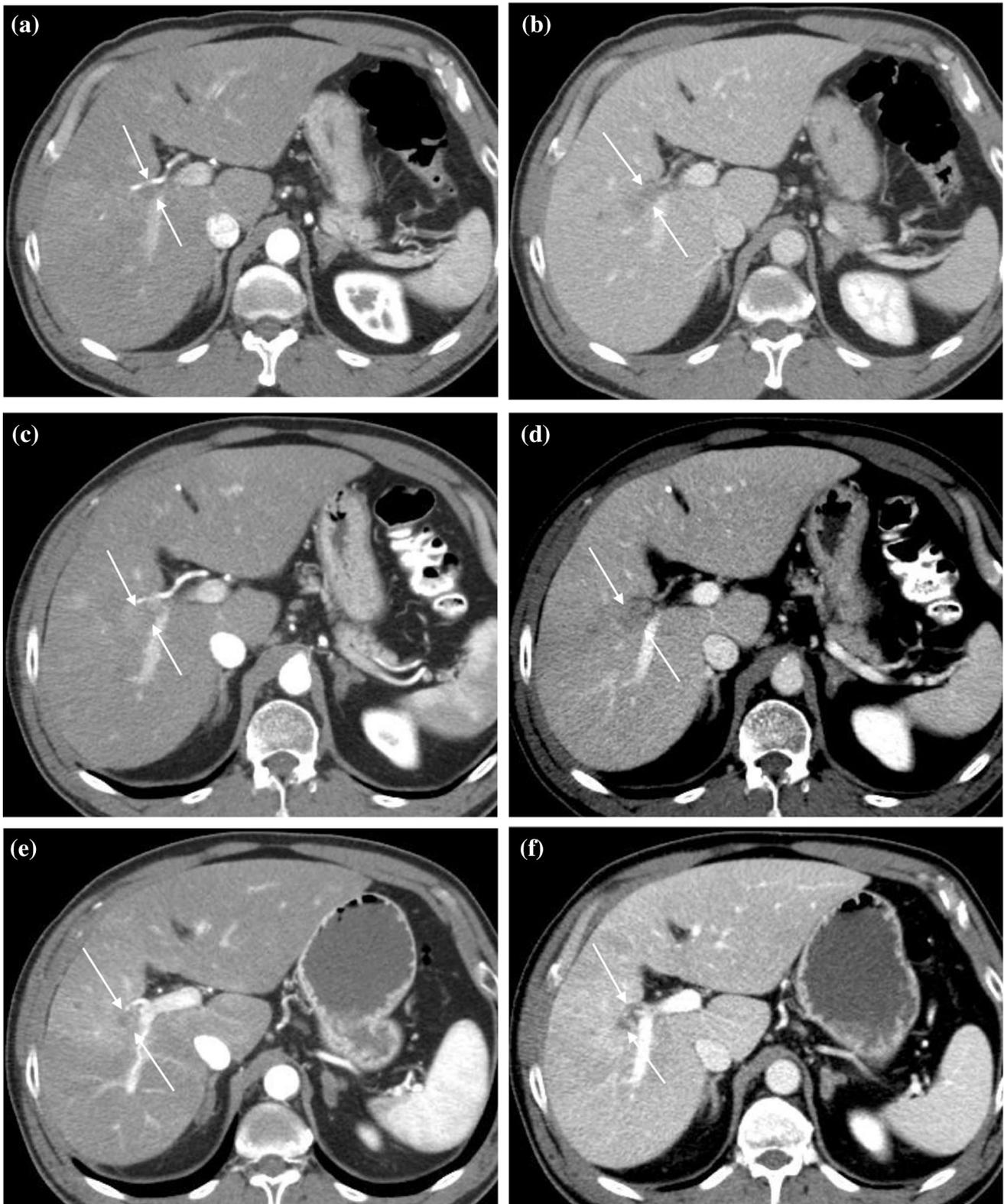
Fig. 1 A 66-year-old male patient with alcoholic cirrhosis and a large exophytic HCC arising posteriorly from segment 6/7 was treated with 45 Gy in 6 fractions SBRT as a bridging therapy awaiting liver transplanting. **a, b** Axial arterial phase (**a**) and delayed phase (**b**) CT images demonstrate a mass (arrow) with heterogeneous arterial-phase

hyperenhancement, delayed phase washout, and multifocal small areas of necrosis. **c, d** Imaging 3 months post SBRT on axial arterial phase (**c**) and delayed phase (**d**) CT images demonstrates a reduction of enhancement of the mass and an increase of the extent of necrosis

to occlusion of the small hepatic vein tributaries and reduced cellularity that has the appearance similar to veno-occlusive disease early post SBRT. These changes are thought to result from endothelial cell damage leading to fibrin deposition. The larger hepatic veins are usually spared. With time, there is resolution of the hyperemia and either regeneration of hepatocellular parenchyma or progression to atrophy and fibrosis [21, 22].

Imaging appearance of HCC response to SBRT

The assessment of HCC response to SBRT requires the evaluation of a combination of factors including: change in target lesion size, change in internal enhancement characteristics, and an estimation of necrosis by assessing the non-enhancing intratumoral region. The imaging appearance gradually changes over time, and therefore, the timing of post-SBRT imaging is also important in the assessment of treatment response.



The reduction in enhancement of liver tumors treated with SBRT often precedes the reduction in tumor size [20]. Price et al reported that the percentage of estimated necrosis

(assessed by non-enhancement within the lesion) was greater than the percentage reduction of the tumor size at each time point of 3 months, 6 months, 9 months and 12 months

Fig. 2 A 59-year-old male with HCC and right portal vein tumor thrombus was treated with SBRT. **a, b** Pre-SBRT axial arterial phase (**a**) and portal venous phase (**b**) CT images demonstrate a tumor thrombus in the right portal vein (arrows), which shows slight arterial-phase hyperenhancement and washout. **c, d** Follow up axial CT at 1-month post SBRT demonstrates an increase in size of the tumor thrombus (**c**) but a reduction in attenuation on the portal venous phase (**d**). **e, f** Further follow-up at 3 months post SBRT showed a reduction in size of the tumor thrombus on the arterial phase (**e**) and portal venous phase (**f**). At further follow-up at 30 months (images not shown), there was complete radiological response, with no measurable disease in the right portal vein

[23]. Brook et al demonstrated that the reduction of tumor enhancement was seen early (on CT performed on days 15–45 post SBRT) and persisted [24]. Lesions that demonstrate reduced enhancement but are stable in size can have significant necrosis at pathological assessment. Therefore, size should play a secondary role to changes in enhancement of an HCC in determining initial response to SBRT. An estimation of necrosis, determined by unenhanced areas within the treated HCC, correlates with response (Fig. 1).

A gradual reduction in size of HCC over months [20] is recognized after SBRT. A previous study demonstrated an average reduction in size of 35% at 3 months, 37% at 6 months, 48% at 9 months and 55% at 12 months post SBRT [23]. Another study demonstrated an average reduction in lesion volume of 24.5% in the first 4 months, 9.8% per month 4–9 months post treatment and 2.7% per month thereafter [24]. The size reduction in HCC treated with SBRT can occur over a long period of time, with a gradual involution over months observed. Lesions treated with SBRT can show progressive necrosis up to 12 months post treatment [23].

The timing of imaging post SBRT is important, as early imaging may be misleading. Early follow-up imaging may demonstrate minimal change in enhancement and no change in tumor size, when performed less than 3 months post SBRT [20]. Reduced attenuation of treated lesions in the portal venous phase relative to the adjacent focal liver reaction [21] has been recognized as an early imaging indicator predicting a favorable outcome. In our experience, an early increase in size does not correspond to long-term tumor progression, while an early reduction in portal venous phase attenuation does appear to correspond to a favorable outcome of tumor response (Fig. 2). Similar changes of reduced enhancement and a gradual reduction in size can be also observed in the treatment of HCC tumor thrombus in the portal vein (Fig. 3).

A recent study of ten HCC lesions treated with SBRT with a successful response (defined as > 90% necrosis at explant pathology or declining alpha-fetoprotein to normalization within 1 year post SBRT) found that four out of ten lesions demonstrated persistent but diminished arterial-phase hyperenhancement [25]. Nine out of ten lesions demonstrated persistent washout and nine out of ten lesions reduced in size at 12 months [25]. This was hypothesized to be due to giant cell

reaction induced by SBRT and gradual reduction over time due to progressive cell death and replacement by fibrosis. Another recent study of 42 HCC treated with SBRT found 39 lesions with complete response (CR) per mRECIST [26]. Four lesions, however, showed CR at 15 months, 16 months, 21 months and 43 months after the treatment. A continuous response can be seen over a long period, even years post SBRT.

Current studies assessing treatment of HCC as bridging therapies to LT utilize a wide variety of criteria including RECIST, mRECIST and EASL, with no current standard criteria for response evaluation. The assessment of HCC response post SBRT, similarly, has not been standardized for uniform reporting. It remains unclear if mRECIST and EASL response criteria are applicable to HCC treated with SBRT [21] because partial necrosis after SBRT involve heterogeneously within the tumor rather than discrete devascularized areas that are usually seen after other local ablative therapies such as radiofrequency ablation. In the area of bridging therapy for those with HCC awaiting LT, it is critical to assess response to SBRT relative to the eligibility for LT and dropout from LT waitlist [27]. Therefore, the detection of disease progression has a higher utility rather than the quantification of response.

Few papers have discussed the imaging changes of HCC treated with SBRT on MRI. A recent study of MRI for post SBRT evaluation for HCC described imaging findings that can predict tumor response. Reduction of hyperintensity on diffusion-weighted imaging (DWI) and T2-weighted imaging was predictive of RECIST responses on subsequent MRI scans [28].

Post-SBRT focal liver reaction

Focal liver reaction refers to the change in imaging appearance of the liver parenchyma adjacent to the SBRT target lesion that lies within the radiotherapy field, corresponding to veno-occlusive disease pathologically. SBRT results in a varied imaging appearance of the adjacent non-target liver that also gradually changes over time. Focal liver reaction should not be mis-diagnosed as tumor progression. It is important to understand typical imaging findings of focal liver reaction and expected changes over time to prevent false-positive diagnosis of tumor progression.

The etiology of focal liver reaction is similar to RILD, but the presence of focal liver reaction on post-SBRT imaging is not related to the development of clinical RILD [21]. Factors that determine the extent of focal liver reaction include SBRT dose and fractionation, prior or concurrent other treatments such as chemoembolization or surgery, and the presence of underlying chronic liver disease [20]. Focal liver reaction has been classified into acute, subacute and chronic

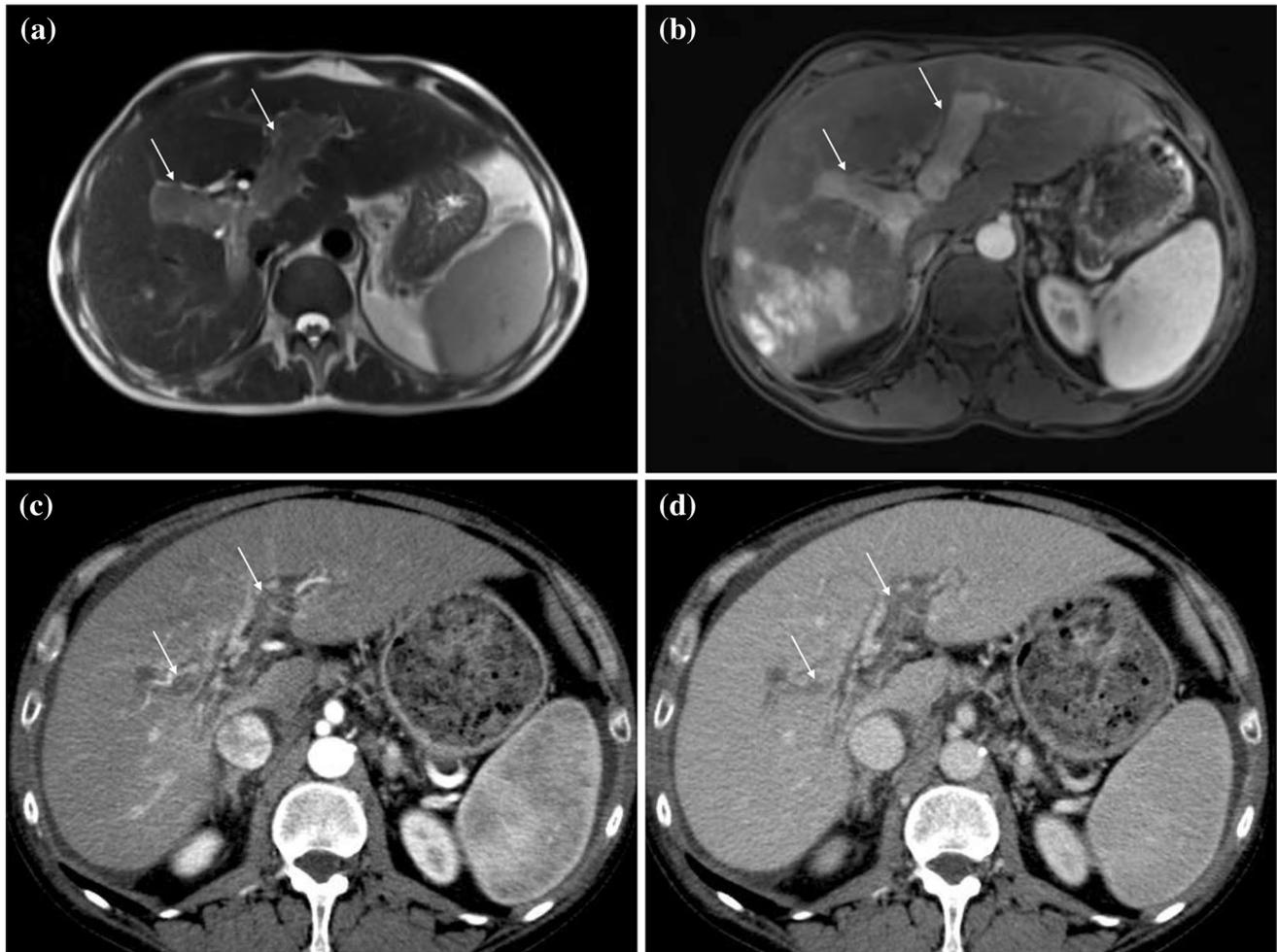


Fig. 3 A 57-year-old male with cirrhosis and advanced HCC in segment 6/7 was treated with SBRT for extensive tumor thrombus in the main, left and right portal veins. **a, b** Axial T2-weighted (**a**) and arterial phase T1-weighted (**b**) MR images demonstrate extensive tumor thrombus in the portal veins isointense to HCC (partly shown in the

right lobe). **c, d** Axial arterial phase (**c**) and portal venous phase (**d**) CT at 1 month post SBRT shows a marked reduction in size and enhancement of the tumor thrombus, with no arterial hyperenhancement remaining

stages based on the time from SBRT, and each stage has different imaging characteristics (Table 1).

The acute stage occurs 1–3 months post SBRT and is characterized by severe sinusoidal congestion due to reduced hepatic vein drainage, with fibrin thrombi within the sinusoids [20]. There is perisinusoidal hemorrhage and reactive hyperemia [20], with hepatocyte atrophy and degeneration in zone 3 pathologically. On imaging, this typically results in hypoattenuation of the liver on unenhanced images [21] that resolves over time. There is arterial-phase hyperenhancement [20] that can persist or fade on the portal venous phase due to reduced portal venous flow (Fig. 4). The affected liver is typically isoattenuating to unaffected liver in the delayed phase. Perilesional changes with either rim-like enhancement and hyperintensity on T2-weighted MR images has been described in the acute phase [28].

The subacute stage occurs 3–6 months post SBRT. Pathologically, there are findings similar to the acute stage but with further obstruction or occlusion of sub-lobar veins [20]. On imaging, this is characterized by hypoattenuation of the parenchyma and hypoenhancement in the portal venous phase with progressive or hyperenhancement in the delayed phase [20, 29], due to obstruction of the central veins and reduced clearing of intravenous contrast (Fig. 5). One study, however, found that at 6 month follow up, peak hyperenhancement was seen in the arterial phase instead of the delayed phase [29], with a peak incidence of hepatic attenuation difference at 3 months post SBRT. This suggests that the division between the acute and subacute stage of focal liver reaction on imaging is not distinct.

Table 1 Imaging changes in HCC treatment response and focal liver reaction post SBRT

Time from SBRT	Typical imaging findings of HCC on CT	Imaging findings of focal liver reaction on CT
1–3 months	-Stable size or mild size—reduction -Mild reduction of enhancement in the arterial-phase and portal venous phases	Acute focal liver reaction -Unenhanced: hypoattenuation relative to background liver -Arterial phase: hyperattenuation in a band-like or wedge-shaped distribution -Portal venous phase: fade or persistent hyperattenuation -Delayed phase: isoattenuation to background liver
3–6 months	-Mild reduction in size -Further reduction of enhancement in the arterial-phase and portal venous phases	Subacute Focal Liver Reaction - Unenhanced: hypoattenuation relative to background liver - Arterial and portal venous phase: hypoattenuation - Delayed phase: progressive enhancement or hyperattenuation
> 6 months	-Further reduction in size -Further reduction of enhancement in the arterial-phase and portal venous phases -Increased delayed-phase enhancement	Chronic focal liver reaction -Regeneration and recovery OR -Delayed-phase hyperattenuation (due to enhancement of bridging fibrosis) and volume loss)

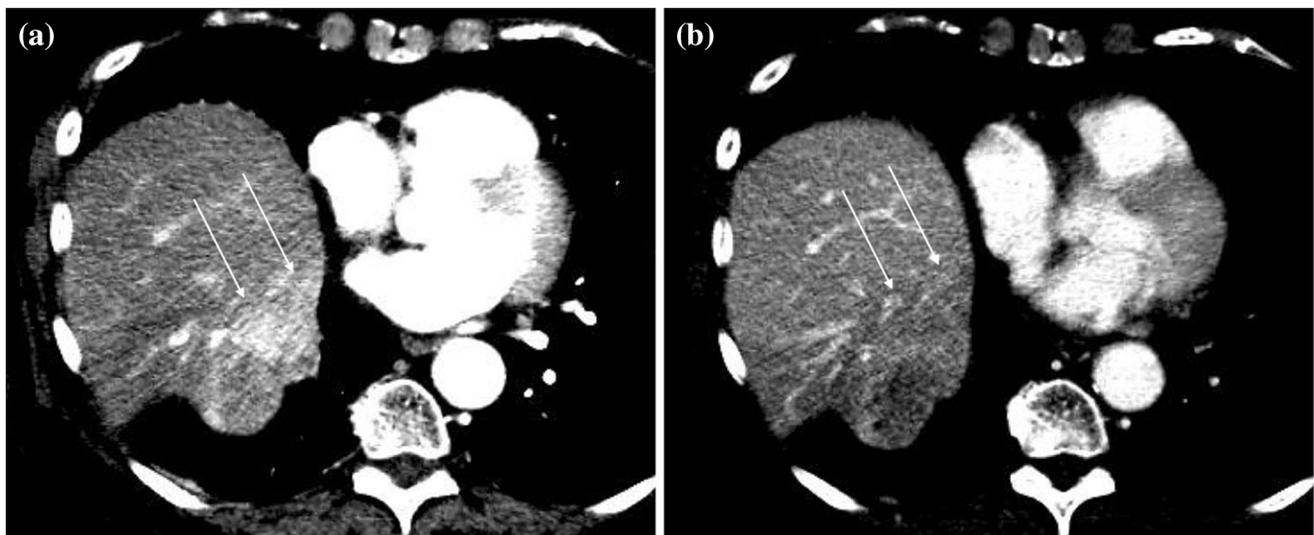


Fig. 4 A 73-year-old male with HCC in liver segment 7 was treated with SBRT. **a, b** Axial arterial phase CT (**a**) 1 month post SBRT demonstrated band like arterial hyperenhancement around the treated

mass that became hypoattenuating on axial portal venous phase CT (**b**) in keeping with the acute phase of FLR

The chronic stage occurs greater than 6 months post SBRT. Pathologically, there is central vein occlusion or fibrosis and collapse of the lobules with distortion [20]. On imaging, this is characterized by either regeneration and recovery or progression to parenchymal atrophy and fibrosis, with resulting contraction (Fig. 6). There is usually hyperenhancement in the delayed phase due to fibrous.

MRI may show hypointensity on gradient-echo sequences due to hemosiderin accumulation in Kupffer cells pathologically [20]. The degree of regeneration of the liver and regain of liver volume may be limited in those with underlying chronic liver disease [20]. Following large volume irradiation, a total reduction in the irradiated liver volume post



Fig. 5 A 58-year-old male patient with a giant HCC replacing the right liver lobe was treated with SBRT. **a, b, c** Follow-up CT imaging at 5 months post SBRT demonstrates reduced size and attenuation of the treated HCC. The adjacent liver demonstrates a well-demarcated area of hypoenhancement on the axial arterial (**a**) and axial portal

venous phase (**b**) CT. In the delayed phase (**c**), this adjacent liver becomes isoattenuating compared to the remainder of the liver parenchyma. There is no mass effect on the traversing vessels. The findings are in keeping with the subacute phase of FLR

Fig. 6 A 50-year-old male patient with advanced left lobe HCC and portal vein thrombus was treated with SBRT. Serial CT imaging was performed **a** prior to SBRT, and **b** at 2 months, **c** at 4 months, **d** at 7 months and **e** at 13 months post SBRT. Selected images from the portal venous phase demonstrate a gradual volume loss and the evolution of band-like hyperattenuation in the treatment window, in keeping with progression to chronic FLR



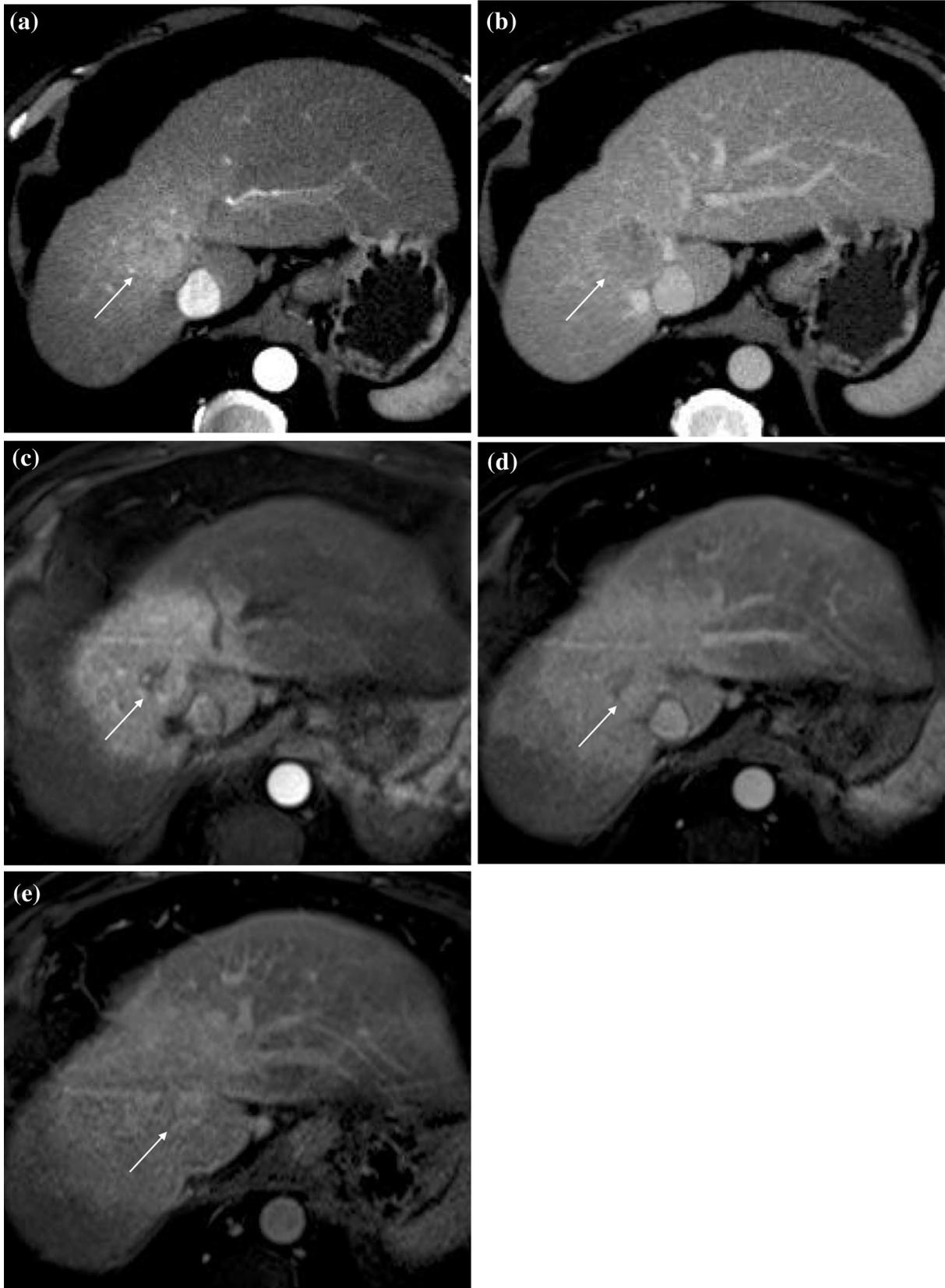


Fig. 7 A 58-year-old male with HCV cirrhosis in segment 8 was treated with 42 Gy in 6 fractions of SBRT as a bridging therapy to liver transplantation. **a, b** Axial arterial phase (**a**) and delayed phase (**b**) CT images at 1 month post SBRT demonstrates a mass (arrow) with arterial-phase hyperenhancement and washout. There is mild pre-lesional arterial-phase hyperenhancement which becomes isoattenuating to the liver in the delayed phase. **c, d, e** 3-month follow-up axial T1-weighted arterial phase (**c**), portal venous phase (**d**) and delayed phase (**e**) MR images demonstrate a large peri-lesional area of hyperenhancement without washout in keeping with focal liver reaction. The treated HCC (arrow) shows reduced, but persistent enhancement that corresponded to 85% tumor necrosis of moderately differentiated HCC with residual areas of tumor interrupted by dense fibrous septae at explant pathology. The adjacent cirrhotic liver demonstrated changes of sinusoidal congestion and obstruction at pathology, corresponding to the changes of acute to subacute FLR seen on imaging

SBRT, to 10% below baseline, even following regeneration, has been observed [21]. Capsular retraction of the liver progresses with time, and a subcapsular location of the target lesion is predictive of long-term capsular retraction [28].

Focal liver reaction typically occurs in a band-like configuration, which is helpful to avoid misinterpretation of hyperenhancement as residual or recurrent disease. The lack of contrast washout and the absence of mass effect on traversing vessels assist in differentiating focal liver reaction from residual or recurrent tumor. Progressive enhancement within the treated site with time correlates to fibrosis within the treated lesion (Fig. 7).

Previous studies have demonstrated that abnormal enhancement occurs around treated liver lesions in all cases post SBRT [23] and there is a significant difference in the liver attenuation before and after treatment [24]. Rim-like arterial and/or portal venous phase enhancement due to focal liver reaction around the treated tumor in the acute and subacute stages [20], should be differentiated from lobulated rim enhancement that can be seen with residual or recurrent disease [21]. Resolution of this enhancement by the chronic stage (6–9 months) [20] and lack of washout [29, 30] should help to differentiate this from residual or recurrent tumor.

Recently, MRI with gadoxetate disodium (Gd-EOB-DTPA; Primovist, Bayer Schering Pharma AG, Berlin, Germany) is commonly used for liver imaging. Focal liver reaction is seen as well-demarcated focal hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, reflecting the degree of decreased hepatic function. This technique is potentially useful to provide a quantitative assessment of radiation-induced liver toxicity and to determine the threshold dose for developing focal liver reaction [31, 32].

Child–Pugh score is a significant factor associated with the type of focal liver reaction observed in the irradiated liver [21]. Higher Child–Pugh scores correlate with persistent changes of focal liver reaction over time and a reduction in liver density in the irradiated field compared to

non-irradiated liver [21, 30]. Hyperenhancement of focal liver reaction in all contrast phases in the chronic stage is more commonly seen in patients with Child–Pugh class A than those with Child–Pugh class B [33]. In addition, arterial-phase hyperenhancement of the target lesion in early post-SBRT period can vary by the severity of cirrhosis [25]. Threshold doses for focal liver reaction have been reported as 30 Gy in 5 fractions for Child–Pugh A and 25 Gy in 5 fractions for Child–Pugh B cirrhosis [32].

Conclusion

SBRT has emerged as an accepted treatment modality for HCC with encouraging outcomes regarding local control and acceptable side effects in selected patients. This has defined new roles for SBRT in the treatment of HCC, presently used either as a primary treatment in patients who are not suitable for other local treatments or as a bridge to liver transplantation. Therefore, more patients will undergo imaging follow-up to assess tumor response. Imaging follow-up of HCC treated with SBRT is challenging due to a combination of the imaging features of response in the lesion and the changes of focal liver reaction in the adjacent non-target liver. In early post-SBRT imaging, the tumor may demonstrate persistent enhancement characteristics of HCC. Imaging before 3 months post-SBRT may underestimate the response. A reduction of tumor size and an increase of tumor necrosis often continue over several months or years after SBRT. Early reduction of tumor enhancement may predict a favorable outcome. With increasing time post SBRT, hyperattenuation around a treated lesion may correspond to focal liver reaction and progressive fibrosis rather than tumor at pathology [24]. Therefore, image interpretation requires caution and knowledge of focal liver reaction to differentiate this from residual or recurrent viable tumor. A close collaboration between the Radiologist and the Radiation Oncologist can be helpful in the interpretation of equivocal findings by evaluating details from previous radiation treatment plans, such as beam incidences and isodose curves.

Currently, there are no validated guidelines for the imaging assessment of post-SBRT HCC tumor response. The assessment of tumor response should include changes in the internal enhancement characteristics of the target lesions correlating with tumor necrosis, and changes in the size of the lesion. Further prospective studies are required to validate imaging biomarkers for post-SBRT assessment and to determine the optimum imaging follow up intervals, depending on the indications for SBRT. Novel imaging modalities enabling the assessment of functional parameters such as positron-emission tomography (PET) or diffusion-weighted MRI also warrant further evaluation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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