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Stereotactic ablative radiotherapy for patients with hepatocellular carcinoma: analysis of post-treatment radiology and explant histology

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BACKGROUND: Stereotactic ablative radiotherapy (SABR) has emerged as a new treatment modality for hepatocellular carcinoma (HCC). Evaluation of tumour responses following SABR are currently based on conventional radiological criteria used for locoregional therapies. Whether these criteria accurately reflect tumour responses following SABR remains unknown. In this study, we provide a direct comparison of post-SABR radiological evaluation and explant histology for patients with HCC who underwent bridging SABR prior to liver transplantation.

METHODS: Patients with HCC who received SABR as bridging therapy prior to liver transplantation (January 2016-December 2022) in a large UK liver transplant centre were included. Post-SABR imaging was reported by two specialist hepato-pancreato-biliary radiologists, and histological examination of the explanted liver was performed by experienced liver histopathologists.

RESULTS: Six patients with residual active HCC received SABR as bridging therapy prior to undergoing liver transplantation in our cohort. Of five patients with viable HCC detected on explant histology, recent radiological evaluation using LI-RADS treatment response criteria had suggested no evidence of residual active HCC for three patients, difficulty delineating residual disease from post-radiotherapy changes for one patient, and accurately identified viable tumour in one patient.

CONCLUSION: In our case series conventional radiological criteria underestimated HCC tumour viability following SABR compared to explant histology. As the role for SABR expands in the management of HCC, caution is needed with radiological interpretation of HCC responses to radiotherapy using standard LI-RADS criteria. Prospective study in a larger cohort is required to identify radiological criteria capable of more conclusively evaluating HCC responses to SABR.

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BACKGROUND

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related death worldwide, with a rising prevalence globally [1]. Treatment options for HCC depend on the tumour size and location, patients' liver function, medical comorbidities, physical fitness and patient choice [2]. For patients with HCC that are listed for liver transplantation, bridging therapies are frequently applied to prevent progression of the tumour outside listing criteria [2].

In recent years, stereotactic ablative radiotherapy (SABR) has been introduced as a new non-invasive treatment option for HCC, in particular as second-line therapy for tumours not suitable for radiofrequency or microwave ablation, or poorly responsive to transarterial chemoembolisation (TACE) [3]. SABR delivers precise high-dose radiation to the tumour, while sparing surrounding healthy liver tissue. While the evidence base for SABR in HCC consists largely of retrospective studies with heterogeneous patient populations, early results appear promising in appropriately selected patients with compensated liver function, showing high rates of local tumour control in the region of 75-90% at three years, and low risks of radiation-induced liver disease [4–9].

More recent data support the use of SABR as a bridging therapy to liver transplantation for patients with HCC [10, 11]. In a retrospective review of 379 patients by Sapisochin et al. bridging SABR demonstrated similar post-transplant outcomes to bridging radiofrequency ablation or TACE [10]. Preliminary data from the first phase two randomised control trial comparing bridging SABR versus TACE for HCC (NCT02182687) suggest that SABR may be associated with fewer inpatient admission days and lower toxicity [12].

Timely assessment of treatment responses in HCC is important. However, since HCC in cirrhotic patients is conventionally assessed by radiological criteria and not biopsy, whether radiological responses following SABR accurately represent histological findings has not been well explored. Examining explants obtained after SABR provides a valuable opportunity for direct comparison.

In this study, we compare radiological evaluation of tumour responses to explant histology in a case series of six patients with

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Table 1. Patient characteristics.

Patient No	Aetiology of cirrhosis, Child Pugh grade/ score	Maximum diameter of HCC lesion	Previous treatment	SABR radiation dose & fractions	Post SABR imaging report (months post SABR)	Time from SABR to transplant	AFP pre and post SABR	Time from post-SABR imaging to transplant	Explant histology report
1	PBC, CPA (6)	2.8 cm	Percutaneous ethanol injections (HCC located next to TIPSS stent)	50 Gy in 5 fractions	**MRI liver (3 months)** – no conclusive evidence of active HCC, subtle enhancement around previously treated tumour, possibly post radiotherapy change. **MRI liver (11 months)** – no significant arterialised abnormality.	12 months	1668 to 3	1 month	One viable hyperplastic nodule (treated lesion measuring 0.7x1cm), and a second well-differentiated HCC 1 cm maximum diameter (not previously seen on imaging).
2	ARLD CP A(6)	3.5 cm	TACE x 2 Sep and Oct 2019	50 Gy in 5 fractions	**CT liver (3 months)** – mild uniform enhancement within treated nodule, reduced in size to 2 cm, no evidence of tumour activity.	6 months	AFP 5 to 8	4 months	4 cm area of scarring with a central nodule 1.6 cm in diameter, moderately differentiated HCC with peri-tumoural vascular invasion.
3	MASLD CP A(5)	4.5 cm	TACE Nov 2019	40 Gy in 5 fractions	**CT liver (2 months) –** hyper-enhancing mass slightly well-defined but increased in size to 5 cm, 1.7 cm arterialised satellite nodule, geographic hyperenhancement in surrounding parenchyma potentially reflects SABR but makes delineation of lesion more challenging.	3 months	AFP 3 to 4	1 month	Single tumour 4.6 cm moderately differentiated HCC. The vast majority of the tumour is viable, with several foci suspicious for vascular invasion.
4	MASLD CP A(6)	3 lesions largest 3.5 cm	TACE Jan 2018	50 Gy in 5 fractions	**MRI liver (3 months)** no convincing active disease, mixed density lesion demonstrates increased T1 signal and no convincing washout, likely to represent post-treatment haemorrhage. **CT (5 months)**– no convincing residual active disease, further two indeterminate arterialised abnormalities. **CT (8 months)**– appearances stable, unchanged from previous.	9 months	AFP 5 to 3	1 month	Four discrete tumours largest 3 cm, all macroscopically similar, in keeping with viable well-differentiated HCC, foci of vascular invasion identified.
5	MASLD CP A(6)	2.7 cm	TACE Jan 2022	50 Gy in 5 fractions	No post-SABR pre-transplant imaging	1 month	3 (no post-SABR result)	n/a	2 ×2.5 cm moderately differentiated HCC viable with no evidence of necrosis.

HCC who received SABR as bridging therapy prior to undergoing liver transplantation.

METHODS

All patients diagnosed with HCC who received SABR as bridging therapy to liver transplantation, between 1 January 2016 to 31 December 2022, at the Queen Elizabeth Hospital Birmingham, were included in the study. Our centre is a large UK tertiary-centre for liver transplantation with specialist expertise in HCC management.

SABR is not routinely performed as bridging therapy to liver transplantation for HCC in the UK, and HCC tumours are not commonly biopsied following treatment, limiting the total sample size.

Data were retrospectively collected on patient demographics, HCC tumour size, tumour number and location and the presence of vascular invasion, as well as patients' liver function, alpha-fetoprotein (AFP) level, and Child Pugh score. Data on previous treatments received, SABR treatment protocols, radiological imaging performed, and liver transplantation were collated (Table 1).

SABR was performed by experienced clinical oncologists. SABR was delivered using a risk-adjusted approach to dose prescription. All patients were treated in five fractions, treating on alternate weekdays, using abdominal compression for motion management and 4D CT for treatment planning. Patients were treated in breath hold using volumetric arc therapy. Total dose was determined by mean liver dose, up to a maximum of 50 Gy.

Post SABR imaging (multiphasic contrast CT or MRI) was planned for an interval of 3 months following treatment. Imaging was reported by specialist hepato-pancreato-biliary radiologists and reviewed in an HCC multidisciplinary meeting for confirmation, using LI-RADS (Liver Imaging Reporting and Data Systems) treatment response algorithm examining tumour necrosis or lack of arterial enhancement in lesions following treatment as markers of treatment response.

Histological examination of the explanted liver and tumoural tissue was performed by experienced liver histopathologists. The histological diagnosis of HCC was made in accordance to World Health Organisation classification [13], with each HCC lesion assessed for size, differentiation, tumour necrosis or viability, and vascular invasion.

RESULTS

Between 1 January 2016 to 31 December 2022, six patients received SABR as bridging therapy prior to undergoing liver transplantation in our centre. Patient characteristics are detailed in Table 1. The median age of the patients was 63 (range 57–68), five patients were male, one female. All had an underlying diagnosis of cirrhosis, the aetiology of cirrhosis was Metabolic-dysfunction associated steatotic liver disease (MASLD) in three patients, Alcohol-related liver disease (ARLD) in one patient, and mixed Met-ALD (MASLD and increased alcohol intake) and Primary biliary cholangitis for one patient each. The diagnosis of HCC had been based on characteristic radiological findings in all cases, encompassing at least one solid liver lesion >1 cm in size with arterial enhancement and delayed washout on multiphasic CT or MRI imaging on a background of cirrhosis [14, 15]. The Child Pugh score prior to SABR treatment ranged between 5 and 6 (grade A), the median number of tumours was 1 (range 1–4), median diameter of the largest HCC tumour was 3.2 cm (range 2.7 cm to 4.5 cm), and median AFP pre-treatment was 5 (range 3 to 1668).

SABR was performed as a second-line therapy due to suboptimal responses to TACE in five patients, and second-line to percutaneous ethanol injections in one patient (who had been unsuitable for ablation or TACE), with residual active HCC noted on radiological assessment (CT or MRI) in all cases prior to SABR. The median prescribed dose was 50 Gy in 5 fractions. SABR was well-tolerated with no significant adverse events noted, and no increase in adhesions or surgical challenges was encountered.

The median time from bridging SABR to liver transplantation was 5 months (range 1–12 months). Post SABR imaging was available in five patients prior to undergoing liver transplantation (Table 1), one patient was transplanted before repeat imaging. The

Table 1. continued

Patient No	Aetiology of cirrhosis, Child Pugh grade/ score	Maximum diameter of HCC lesion	Previous treatment	SABR radiation dose & fractions	Post SABR imaging report (months post SABR)	Time from SABR to transplant	AFP pre and post SABR	Time from post-SABR imaging to transplant	Explant histology report
6	ARLD and MASLD CP A(5)	2.7 cm	TACE March 2022	45 Gy in 5 fractions	**CT (2 months)** – focus of residual persistent arterial hyperenhancement at treated lesion, continued follow-up recommended to differentiate residual disease from post-treatment change.	4 months	242 to 107	2 months	1.6 cm moderately differentiated HCC, no vascular invasion.

PBC primary biliary cholangitis, *ARLD* alcohol-related liver disease, *MASLD* metabolic dysfunction-associated steatotic liver disease, *HBV* Hepatocellular B Virus, *TIPSS* transjugular intrahepatic portosystemic shunt, *AFP* alpha fetoprotein.

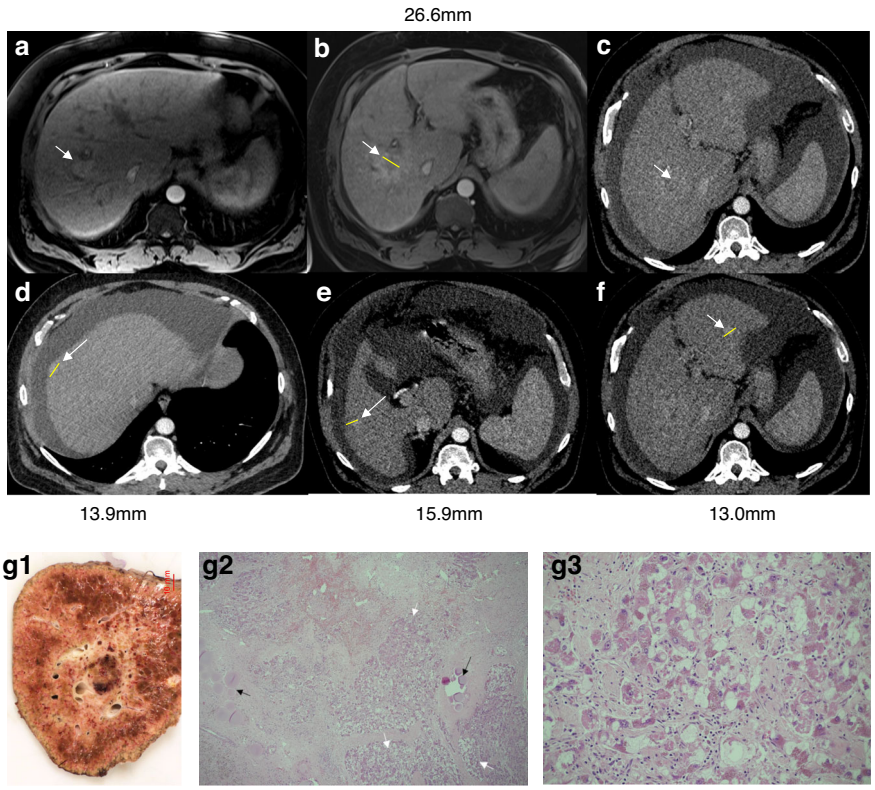

Fig. 1 Multiphase contrast imaging and corresponding explant histology. Patient 4 **a** Pre-SABR MRI showing arterially enhancing central Segment 8/5 HCC lesion; (**b**) 3 months post-SABR CT showing partial response and treatment related changes, with central necrosis and thin rim-like peripheral enhancement; (**c**) 8 months post-SABR CT showing very inconclusive arterial phase enhancement; (**d**, **e**, **f**) 8 months post-SABR CT showing further 3 arterialised liver lesions with no convincing washout LIRADS 3. (G1) Macroscopic slice of liver showing tumour with surrounding fibrosis and cirrhotic liver; (G2) Low-power haematoxylin and eosin staining of tumour showing fibrosis, TACE embolization material (black arrows) and multiple nodules of viable HCC (white arrow). (G3) High power view of viable tumour.

median interval between post-SABR imaging and liver transplantation was 1 month (range 1–4 months). Multiphasic contrast CT was the choice of imaging in three patients and MRI in two patients, with imaging performed at a median time-frame of 3-months post SABR treatment.

Post-SABR imaging was available in five patients and was reported by experienced radiologists as showing no evidence of residual active HCC in three patients (Table 1, Fig. 1), indeterminate hyperenhancement with difficulty delineating residual disease from post-radiotherapy changes in one patient (Fig. 2), and active HCC with increased tumour size in one patient. In all five of these cases, viable HCC tumour was subsequently detected in the explant histology.

DISCUSSION

SABR is emerging as a valuable treatment modality for HCC. In this study we directly compare post-SABR radiological and histological evaluation of treatment responses for patients with HCC. In our case series of six patients, we show that radiological evaluation following SABR under-represented residual tumour activity compared to explant histology.

Accurate assessment of treatment responses in HCC is crucial to facilitate timely treatment decisions, and prevent eligible patients progressing outside liver transplant criteria. Tumour responses are conventionally assessed by a reduction in arterial enhancement and decrease in tumour volume on multiphasic CT or MRI [16, 17]. The commonly used mRECIST and LI-RADS treatment response criteria measure the diameter of viable arterially enhancing tumour components and show good prognostic value for HCC treated with locoregional therapy [16–18]. However, whether these criteria are applicable to HCC treated with SABR remains uncertain.

Additional challenges of differentiating viable tumour from radiotherapy-related changes are also present, as persistent arterial hyperenhancement is commonly observed on imaging within the first few months following SABR and in previous studies has not correlated with the risk of local recurrence [4]. In most cases in our cohort, subtle hyperenhancement within the treated lesion had been described on post-SABR imaging, but was not associated with washout on portovenous phase imaging and could not conclusively be differentiated from post-radiotherapy changes. Imaging performed at an earlier 6–8 week interval did not provide additional benefit over a planned 3-month post-treatment imaging interval, due to the difficulties delineating residual disease from post-radiotherapy appearances.

Up to 30% of patients with HCC listed for transplantation are delisted due to progressive disease [19]. An emerging body of literature supports SABR as a promising bridging therapy to achieve tumour control while awaiting liver transplantation [10–12], although the rates of complete tumour necrosis on explant histology have appeared modest [10, 20–22]. Previous case series of patients with HCC transplanted following bridging SABR in Mount Sinai USA ($n = 27$) [20], Germany ($n = 4$) [21], Rochester USA ($n = 24$) [22], and Canada ($n = 30$) [10], have demonstrated complete tumour necrosis on explant histology for: 14% (versus a collective estimate of 30% by radiology), 25%, 29%, and 13% of treated patients respectively [10, 20–22].

To our knowledge, our study is the first UK study comparing radiological interpretation and explant histology of tumour responses for patients with HCC treated with bridging SABR,

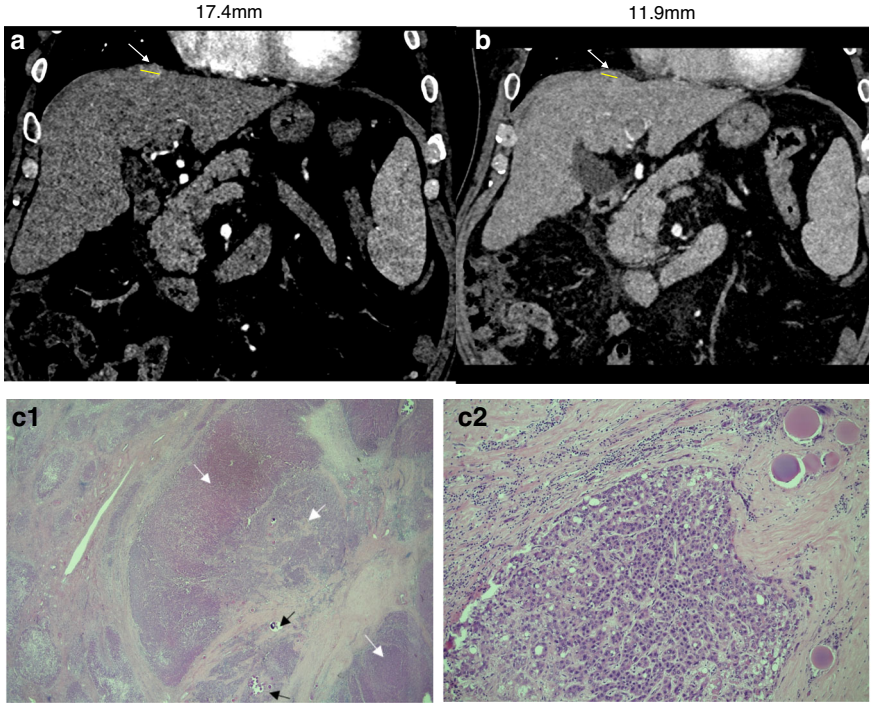

Fig. 2 Multiphase contrast imaging and corresponding explant histology. Patient 6**. a** Pre-SABR CT showing arterially enhancing Segment 4 HCC; (**b**) 3 months post-SABR CT showing reduction in the lesion size with minimal residual enhancement; (C1) Low power haematoxylin and eosin staining of tumour showing fibrosis, embolization material (black arrows), viable tumour (white arrows), and a background of cirrhosis (left hand side of image). (C2) Higher power view showing viable tumour (embolization material present on right hand side of image).

and the first study to provide a detailed side-by-side comparison of the radiology and histology. In our cohort, a significant reduction in tumour size by >1 cm occurred in three out of six patients post SABR treatment, accompanied by a marked reduction in AFP in two cases. However, all six treated patients in our cohort still had viable tumour detected in explant histology. This may be due to the relatively short time-frame between SABR and transplantation in our cohort (median 5 months), as while we would expect early reductions in tumour volume by 3 months post SABR [23], tumour necrosis has been shown to increase for up to 12 months in primary HCC tumours treated with SABR [23]. The short interval between post SABR imaging and subsequent transplantation (median 1 month) makes it unlikely that new local tumour recurrence had occurred during this interval.

While our data suggest that greater caution is needed with radiological interpretation of post-SABR tumour activity, this would not have affected the decision to transplant in our cohort. Radiological assessment provided appropriate reassurance of tumour control and no patients had progressed outside transplant criteria on explant histology. However, if our waiting times from treatment to transplantation had been longer, the need for more accurate stratification of residual tumour activity post-SABR may have been more imperative.

Our study also raises a broader question over the accuracy of post-treatment imaging interpretation for patients with early-stage HCC who receive SABR treatment alone and not as a bridge to liver transplantation. Histological evaluation of treatment response is rarely obtained for this cohort, and currently there are no definitive radiological criteria validated for evaluation of tumour activity following SABR, leading to potential risks for inaccurate classification. In our centre, we adopt a protocol of serial 3-monthly multiphasic contrast MRI or CT imaging for the first 12 months post-SABR (and 6-monthly thereafter) for surveillance for lesion changes, together with AFP monitoring, to help facilitate timely treatment decisions.

This case series is limited by its retrospective nature and small sample size. Despite our seven-year recruitment period, SABR is not routinely performed as a bridging therapy to liver transplantation for HCC in the UK, and HCC tumours are not commonly biopsied in cirrhotic patients due to concerns over bleeding and tumour seeding, albeit these risks have recently been demonstrated to be low [24], thus routine access to histology for examination in a larger cohort was not available. Future study in a larger patient cohort across multiple liver transplant centres is required to validate our findings.

In conclusion, we find that conventional radiological evaluation following SABR underestimated residual HCC tumour activity compared to explant histology. Prospective study is required to identify radiological criteria capable of more conclusively evaluating HCC responses to radiotherapy.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

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AUTHOR CONTRIBUTIONS

NZ and SS contributed to the study concept and design. NZ collated and analysed the data and drafted and revised the manuscript. RM, OC, JG, TS, SS contributed to data collection, review and editing of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Queen Elizabeth Hospital Birmingham UK (Clinical audit registration and management system reference number 22814). Participants' consent was not required for approval as presented data are all anonymised.

ADDITIONAL INFORMATION

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