Presence of tumour capsule on contrast-enhanced CT is associated with improved outcomes of stereotactic body radiation therapy in hepatocellular carcinoma patients

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ORIGINAL ARTICLE

Presence of tumour capsule on contrast-enhanced CT is associated with improved outcomes of stereotactic body radiation therapy in hepatocellular carcinoma patients

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Abstract

Purpose Stereotactic body radiation therapy (SBRT) is a novel local therapy for the treatment of hepatocellular carcinoma (HCC). While effective, there is currently no reliable radiological marker to guide patient selection. In this study, we investigated the prognostic value of capsule appearance on contrast-enhanced computed tomography (CT) for patients undergoing SBRT.

Materials and methods Between 2006 and 2017, 156 consecutive patients with Child–Pugh score class A/B and HCC ≥ 5 cm who underwent SBRT were retrospectively analysed. Baseline triple-phase CTs of the abdomen were reviewed for the presence of capsule appearances and correlated with objective response rate (ORR), overall survival (OS) and pattern of treatment failure.

Results Capsule appearance on CT was present in 83 (53.2%) patients. It was associated with improved ORR by Response Evaluation Criteria in Solid Tumours (RECIST) (60.2 vs. 24.7%, $p < 0.001$) and Modified Response Evaluation Criteria in Solid Tumours (mRECIST) (78.3 vs. 34.2%, $p < 0.001$). The presence of a capsule was also associated with superior 2-year local control (89.1 vs. 51.4%, $p < 0.001$) and 2-year OS (34.1 vs. 14.8%, $p < 0.01$). Hepatic out-field failure was the dominant mode of progression, which was less common in patients with intact capsule (54.2 vs. 60.3%, $p = 0.01$).

Conclusion Capsule appearance on CT could potentially be a non-invasive prognostic marker for selecting HCC patients to undergo SBRT. A larger cohort is warranted to validate our findings.

Keywords Precision medicine · Radiological prognostic marker · Imaging · Local control · Overall survival

Co-first authors: Siu Hin Mak and Sean Man Natalie Wong are co-first authors of this manuscript.

Availability of data and material Data are available from the corresponding author upon reasonable request.

Code availability Not applicable

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Introduction

Hepatocellular carcinoma (HCC) represents 80–85% of primary hepatic malignancies worldwide [1, 2]. Due to insidious onset of the disease, patients often present late, with median survival of 6 to 20 months from diagnosis [3]. Stereotactic body radiation therapy (SBRT) is an emerging non-invasive treatment modality for HCC patients when curative resection is not possible. It delivers highly directional radiation doses to maximize local tumour regression and minimize insult to neighbouring healthy tissues. Among patients with small-sized HCC, studies have demonstrated that SBRT achieves similar local control to that seen in those undergoing resection or radiofrequency ablation (RFA) [4, 5]. For tumours beyond the limits of curative interventions, emerging data show that SBRT is more efficacious than transarterial chemoembolization (TACE) in controlling sizeable tumours [6].

While most literature supports the clinical efficacy of SBRT, the radiosensitivity of HCC and clinical outcomes of patients vary, particularly among those with sizable tumours. Recent meta-analysis has shown the 3-year local control rate to be >85% in HCC <5 cm, compared to only 59.7% in HCC ≥5 cm [7]. To date, there is no reliable radiological prognostic marker that could aid patient selection for SBRT. There is a need to better stratify patients to identify those who are most likely to respond to SBRT, so as to avoid futile interventions.

Tumour capsule around HCC is a relatively common radiological observation on computed tomography (CT), estimated to be present in 42% of tumours larger than 5 cm [8, 9]. It is a major diagnostic feature for HCC in the Liver Imaging Reporting and Data System (LI-RADS), associated with a lower incidence of direct tumour invasion, vascular permeation and microsatellite formation, and better recurrence-free survival in surgically resected patients [10–14]. Histologically, it represents expansile growth of the tumour, indicating a less aggressive nature of these HCCs [15]. Thus, we hypothesize that the presence of tumour encapsulation on imaging can serve as an important imaging biomarker of favourable cell biology and may help in the selection of patients for SBRT. In this study, patients with large-sized advanced HCC who had undergone SBRT in the Tuen Mun Hospital were retrospectively evaluated for the presence or absence of tumour capsule, and this was correlated with treatment response and survival.

Materials and methods

Patient population

Institutional review board (IRB) approval (NTWC/CREC/18064) was obtained for this single-centre retrospective analysis of a prospectively collected observational cohort study. Consecutive patients with HCC receiving SBRT in Tuen Mun Hospital were recruited. Inclusion criteria for SBRT were as follows: (i) radiological or histological diagnosis of HCC in patients who were ineligible for or refractory to curative/surgical interventions, or patients who refused curative/surgical treatment; (ii) tumour size >5 cm; (iii) ≥700 mL of uninvolved liver; (iv) Eastern Cooperative Oncology Group (ECOG) performance score ≤2; (v) Child–Pugh (CP) score of A5 to B7; (vi) adequate organ function. The exclusion criteria for SBRT included (i) diffuse type of HCC and (ii) >5 tumour nodules. Extrahepatic metastases were allowed only if primary disease burden originated from intrahepatic tumour bulk.

These patients were managed by a liver multidisciplinary team consisting of radiation oncologists, surgeons and radiologists with over 10 years of experience in treating HCC patients. All patients were followed up weekly during treatment, 2-weekly for the first 2 months, monthly for the third month, 3-monthly for the first 2 years and 6-monthly thereafter. Physical examination and liver function tests (LFT) were performed every visit. Additional medical attention was also available at outpatient clinics upon patient request. A triphasic liver CT scan was done every 3 months in the first year and every 6 months thereafter.

A total of 156 patients were eligible for the study and all were included in survival analyses. Baseline patient, tumour and treatment characteristics were retrieved from the electronic patient record (ePR). Pre-SBRT vascular invasion was defined as any macroscopic left/right hepatic portal vein or inferior vena cava invasions on staging CT. Distant metastasis referred to dissemination to any structure other than the liver, which included nodal involvement. Single longest diameter of the largest HCC lesion was evaluated per Response Evaluation Criteria in Solid Tumours (RECIST) criteria v1.1 [16]. Other parameters such as age, sex, alpha fetoprotein (AFP) levels, CP score and aetiological factors were also collected.

Computed tomography acquisition and image analysis

Triple-phase contrast-enhanced CT images were acquired with a Philips Brilliance 16 CT Scanner (Philips Medical Systems, Eindhoven, the Netherlands) in 0.6–5.0 mm slice thickness. Peak voltage of 120 kVp was used with varying tube currents (mA). Gantry rotation time was 0.27 s

with field of view of 512 mm. Detector collimations were 1.25 mm with table speed per rotation at 45 mm. Pitch of 0.938 was used. Reconstruction interval of 1.25 mm was used for image viewing and interpretation. Matrix size was 512 × 512. Arterial phase was captured with bolus tracking once abdominal aorta reached 100 Hounsfield units, whereas portal venous phase was 75 s and delayed phase 3 min after arterial phase was triggered.

HCC capsule appearance was defined as a peripheral rim of smooth hyperenhancement surrounding background tumour nodules in portal venous and/or delayed phase on triphasic CT imaging. The capsule had to have a thickness ≥ 2 mm and surround ≥ 80% of the tumour nodule border to be considered present [17–19]. Regarding patients with > 1 intrahepatic lesion treated by SBRT, only the largest HCC nodule was referenced and interpreted. Capsule status was analysed on a per patient basis. Image analysis was performed by two experienced clinicians who are core members of the multidisciplinary team. Any discrepancies were discussed and resolved by consensus.

SBRT responses were assessed by the Response Evaluation Criteria in Solid Tumours (RECIST) criteria v1.1 and the modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria [16, 20]. Objective treatment responses were categorized into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Stereotactic body radiation therapy

Patients were immobilized via a vacuum foam bag (VacLokTM; MEDTEC, IA, USA). Imaging was performed on contrast CT. Gross tumour volume (GTV) was defined as tumour focus that was visualized on contrast imaging together with expansion to include the lipiodol stained area if any[1]. No margin was added to GTV in forming the clinical target volume (CTV). Breath-hold CT or four-dimensional CT was used to individualize the internal target volume and/or PTV, as described in our previous work[2]. The individualized PTV margins were formulated to compensate for respiratory motion and set-up errors. Motion management was achieved with gating (10%), active breathing control (30%) or abdominal compression (60%).

The total dose was prescribed to the 90% isodose line in 4 Gy per fraction for 6–10 fractions (Fr). The median BED_{10} was 32.7 Gy (range 28–46.7 Gy). The goal was to give a highest possible dose with respect to normal tissue constraints. Normal liver could receive a 2-Gy equivalent dose with α/β ratio = 3 ($EQD2_3$) of 30 Gy < 40% and mean dose < 28 Gy. Other organs at risk (OAR) including luminal gastrointestinal structures, gall bladder, heart, ribs and kidney(s) were also taken into consideration.

Evaluation and statistical analysis

The prognostic value of an intact tumour capsule was evaluated with four distinct endpoints, namely objective response rate (ORR), local control (LC), progression-free survival (PFS) and overall survival (OS). Objective response rate was defined as the proportion of patients reaching CR or PR after SBRT, assessed by means of the RECIST criteria v1.1 and mRECIST criteria. Local control was defined as the lack of progressive disease within the PTV. Progression-free survival was calculated from the date of SBRT commencement to the date of progressive disease or death, whichever occurred earlier. Any new lesion(s) in liver developing outside the PTV was labelled as an intrahepatic out-of-field failure. Vascular metastasis included any macroscopic left/right hepatic portal vein or inferior vena cava invasions. Distant metastasis referred to dissemination to any structure other than the liver, which included nodal involvement. Overall survival was defined as the period from the start date of SBRT to the date of death or last follow-up.

Chi-square and ANOVA (analysis of variance) tests were used to compare categorical and interval variables, respectively. LC and OS estimates were interpreted from Kaplan–Meier survival curves. Log-rank test discovered any potential prognostic factors. Significant factors identified during univariate analysis were subjected to multivariable analysis by Cox proportional hazards model to determine if capsule appearance was an independent prognostic marker of LC and OS. Statistical analysis was performed using statistical software (SPSS version 26.0, released 2019; IBM Corp., Armonk, NY, USA). Significant differences were defined at $p < 0.05$.

Results

Patient and treatment characteristics

Patient characteristics are summarised in Table 1. The 156 patients enrolled in the study were mainly male ($n = 132$, 84.6%) with a median age of 61 years (range 29–85 years). The commonest underlying liver disease was hepatitis B infection ($n = 113$, 72.4%). The median single longest diameter of the largest HCC lesion was 12.9 cm (range 5.1–25.7 cm) and 54.5% ($n = 85$) patients

[1] Lipiodol staining was due to previous TACE. Only one fifth of patients had received TACE before, and the proportion of patients treated with TACE were balanced in the two groups.

[2] One of the patients in [21] was included in the current manuscript. A small proportion of patients ($n = 24$) in the current manuscript have also been reported in [22].

Table 1 Patient, tumour and treatment characteristics

Characteristics	Overall population, *n* (%) *n* = 156	Capsule present, *n* (%) *n* = 83	Capsule absent, *n* (%) *n* = 73	*P*-value
Age, years				
Median	61	62	60	$p = 0.55$
Range	29–85	41–85	29–83	
Sex				
Male	132 (84.6)	67 (80.7)	65 (89.0)	$p = 0.15$
Female	24 (15.4)	16 (19.3)	8 (11.0)	
Aetiology				
Hepatitis B	113 (72.4)	59 (71.1)	54 (74.0)	$p = 0.69$
Hepatitis C	5 (3.2)	4 (4.8)	1 (1.4)	$p = 0.22$
Alcohol	3 (1.9)	1 (1.2)	2 (2.7)	$p = 0.49$
Multiple aetiologies	17 (11.0)	8 (9.6)	9 (12.3)	$p = 0.59$
None	18 (11.5)	11 (13.3)	7 (9.6)	$p = 0.48$
ECOG				
0	43 (27.6)	17 (20.5)	26 (35.6)	$p = 0.51$
1	93 (59.6)	54 (65.1)	39 (53.4)	
2	20 (12.8)	12 (14.5)	8 (11.0)	
BCLC stage				
A	36 (23.1)	23 (27.7)	13 (17.8)	$p = 0.15$
B	28 (17.9)	11 (13.3)	17 (23.3)	
C	92 (59.0)	49 (59.0)	43 (58.9)	
Vascular invasion				
No	107 (68.6)	64 (77.1)	43 (58.9)	$p = 0.02$
Yes	49 (31.4)	19 (22.9)	30 (41.1)	
Extrahepatic metastasis				
No	109 (69.9)	53 (63.9)	56 (76.7)	$p = 0.08$
Yes	47 (30.1)	30 (36.1)	17 (23.3)	
Number of lesions				
Solitary ($n = 1$)	85 (54.5)	54 (65.1)	31 (42.5)	$p = 0.06$
Uninodular ($n = 2$-3)	27 (17.3)	17 (20.5)	10 (13.7)	
Multinodular ($n > 3$)	44 (28.2)	12 (14.5)	32 (43.8)	
Baseline AFP (ng/mL)				
Median	565.5	338	544	$p = 0.73$
Range	1.1–800000.0	1.1–800000.0	2.0–800000.0	
Child–Pugh score				
A5	95 (60.9)	58 (69.9)	37 (50.7)	$p = 0.50$
A6	34 (21.8)	16 (19.3)	18 (24.7)	
B7	27 (17.3)	9 (10.8)	18 (24.7)	
Single longest diameter of largest lesion, cm				
Median	12.9	14.7	10.0	$p < 0.01$
Range	5.1–25.7	6.0–25.7	5.6–19.3	
GTV volume, cm³				
Median	900.8	1176.9	491.0	$p < 0.01$
Range	41.0–3990.7	41.0–3642.0	43.4–3990.7	
PTV size, cm³				
Median	1257.0	1700.4	636.0	$p < 0.01$
Range	43.3–5266.0	84.0–4657.5	43.3–5266.0	
Prescription dose, Gy (EQD2, α/β = 10)				
Median	32.7	28.0	32.0	$p = 0.17$
Range	28.0–46.7	24.0–40.0	24.0–40.0	
Prior treatment				
Nil[a]	118 (75.6)	72 (86.7)	46 (63.0)	$p = 0.23$
Surgery	2 (1.3)	2 (2.4)	0 (0.0)	N/A
Radiofrequency ablation	4 (2.6)	0 (0.0)	4 (5.5)	N/A
TACE	32 (20.5)	9 (10.8)	23 (31.5)	$p = 0.23$

ECOG Eastern Cooperative Group performance status, *BCLC* Barcelona Clinic Liver Cancer, *AFP* alpha fetoprotein, *GTV* gross tumour volume, *PTV* planning target volume, $EQD2_{10}$ radiation dose in 2-Gy equivalent (EQD2, α/β = 10), *TACE* transarterial chemoembolization

[a]Nil means that patients received no other forms of treatment before SBRT

had a solitary tumour. The median prescription dose in 2-Gy equivalents using α/β = 10 ($EQD2_{10}$) was 32.7 Gy (range 28.0–46.7 Gy). Median GTV was 1176.9 cm³ and 491.0 cm³ for the encapsulated and unencapsulated groups, respectively, while median planning target volume (PTV) was 1700.4 cm³ and 636.0 cm³, respectively. Around 75% ($n = 118$) of patients were treatment naïve. The baseline characteristics of the patients are detailed in Table 1.

Of 156 enrolled patients, 83 patients (53.2%) had capsule appearance. The encapsulated group had less baseline vascular invasion (22.9 vs. 41.1%; $p = 0.02$) and larger HCC lesions (14.7 vs. 10.0 cm; $p < 0.01$), while there were no significant differences in other baseline characteristics.

Survival

In total, 139 patients (89.1%) had passed away at the time of analysis. The median follow-up time of the entire cohort was 10.5 months (range 0.3–110.4 months), and that of the surviving patients was 34.6 months (range 13.6–131.7 months). Encapsulated HCC was associated with better median survival as well as 1-year and 2-year OS rates (13.6 vs. 7.5 months, 53.9 vs. 35.5% and 34.1 vs. 14.8%, respectively, $p < 0.01$; Fig. 1b). Likewise, an intact capsule was an independent prognosticator of OS (HR: 0.55, 95% CI 0.38–0.79, $p < 0.01$). Other independent positive prognostic factors included the absence of extrahepatic metastasis, low AFP level (< 400 ng/mL), small number of lesions (≤ 2) and small tumour size (< 15 cm; Table 2).

Table 2 Univariate and multivariate analyses for prognostic markers of local control and overall survival

	UVA			MVA		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Local control						
Age (<60 vs. ≥60)	1.67	0.79–3.52	0.18	–	–	–
Sex (male vs. female)	1.45	0.50–4.22	0.49	–	–	–
Aetiology (hepatitis B vs. non-hepatitis B)	1.25	0.53–2.94	0.61	–	–	–
ECOG (0–1 vs. 2)	1.30	0.39–4.30	0.67	–	–	–
Vascular invasion (yes vs. no)	3.03	1.44–6.38	<0.01	2.84	1.33–6.07	<0.01
Extrahepatic metastasis (yes vs. no)	0.82	0.33–2.03	0.66	–	–	–
AFP level (<400 vs. ≥400 ng/ml)	0.45	0.21–0.97	0.04	0.39	0.18–0.88	0.02
CP class (A vs. B)	0.86	0.30–2.48	0.78	–	–	–
Number of lesions (1–2 vs. 3–5)	0.40	0.19–0.84	0.02	0.48	0.22–1.04	0.06
Size of lesion (<15 cm vs. ≥15 cm)	0.81	0.38–1.77	0.60	–	–	–
Capsule (yes vs. no)	0.14	0.06–0.36	<0.01	0.16	0.06–0.40	<0.01
Overall survival						
Age (<60 vs. ≥60)	1.16	0.83–1.63	0.39	–	–	–
Sex (male vs. female)	1.54	0.97–2.45	0.07	–	–	–
Aetiology (hepatitis B vs. non-hepatitis B)	1.23	0.85–1.79	0.27	–	–	–
ECOG (0–1 vs. 2)	1.07	0.66–1.75	0.77	–	–	–
Vascular invasion (yes vs. no)	1.26	0.87–1.81	0.22	–	–	–
Extrahepatic metastasis (yes vs. no)	1.69	1.17–2.43	0.01	1.55	1.06–2.28	0.02
AFP level (<400 vs. ≥400 ng/ml)	0.47	0.34–0.67	<0.01	0.48	0.34–0.68	<0.01
CP class (A vs. B)	0.68	0.44–1.05	0.08	–	–	–
Number of lesions (1–2 vs. 3–5)	0.57	0.40–0.81	<0.01	0.66	0.45–0.97	0.03
Size of lesion (<15 cm vs. ≥15 cm)	0.62	0.44–0.87	<0.01	0.61	0.43–0.89	<0.01
Capsule (yes vs. no)	0.62	0.44–0.86	<0.01	0.55	0.38–0.79	<0.01

ECOG Eastern Cooperative Group performance status, *AFP* alpha fetoprotein, *CP* Child–Pugh class, *UVA* univariate analysis, *MVA* multivariate analysis, *HR* hazard ratio, *CI* confidence interval

Table 3 Comparison of patterns of failure in patients with or without capsule

	Capsule present *n* (%)[a]	Capsule absent *n* (%)[a]	*P*-value
No progression	13 (15.7)	4 (5.5)	$p=0.11$
Hepatic in-field failure	6 (7.2)	22 (30.1)	$p<0.01$
Hepatic out-field failure	45 (54.2)	44 (60.3)	$p=0.01$
Vascular invasion	6 (7.2)	3 (4.1)	$p=0.60$
Distant metastasis	37 (44.6)	21 (28.8)	$p=0.27$

[a]Sum not equal to 100% as some patients had multiple sites of progression

There was a trend suggesting that encapsulated tumour was associated with better 1-year and 2-year PFS (33.8 vs. 19.5%, 20.6 vs. 14.6%, respectively, $p=0.08$; supplementary Fig. 1). The median time to progression was 5.3 months (95% CI: 3.4 months–7.1 months) and 3.7 months (95% CI 3.2 months–4.3 months) for encapsulated and unencapsulated HCC tumours, respectively.

Pattern of failure

Hepatic out-field failure represented the dominant mode of treatment failure ($n=89$, 57.1%) and patients with encapsulated tumours were less likely to have both hepatic out-of-field failure (54.2 vs. 60.3%, $p=0.01$) and in-field failure (7.2 vs. 30.1%, $p<0.01$). Similar incidences of vascular invasion and distant metastases were observed (Table 3).

Objective response rate and local control

The ORR per best RECIST response was 60.2% for the encapsulated group versus 24.7% for the unencapsulated group ($p<0.001$). Capsule appearance was associated with a higher proportion of radiological response (CR/PR/SD/PD: 0.0%/60.2%/32.5%/3.6% vs. 0.0%/24.7%/37.0%/16.4%, $p<0.001$). Similarly, the ORR per best mRECIST response was 78.3% and 34.2%, respectively ($p<0.001$). Capsule appearance was also associated with radiological response (CR/PR/SD/PD: 3.6%/74.7%/14.5%/3.6% vs. 4.1%/30.1%/27.4%/16.4%, $p<0.001$) (Table 4). Notably, there were 13 patients (15.7%) in the encapsulated

Table 4 Comparison of treatment response and objective response rates (stratified by capsule status)

	Capsule present, *n* (%) *n* = 83	Capsule absent, *n* (%) *n* = 73	*P*-value
Best RECIST response			
CR	0 (0.0)	0 (0.0)	*P* < 0.001
PR	50 (60.2)	18 (24.7)	
SD	27 (32.5)	27 (37.0)	
PD	3 (3.6)	12 (16.4)	
Lack follow-up data	3 (3.6)	16 (21.9)	
	ORR: 60.2%	*ORR: 24.7%*	
Best mRECIST response			
CR	3 (3.6)	3 (4.1)	*P* < 0.001
PR	62 (74.7)	22 (30.1)	
SD	12 (14.5)	20 (27.4)	
PD	3 (3.6)	12 (16.4)	
Lack follow-up data	3 (3.6)	16 (21.9)	
	ORR: 78.3%	*ORR: 34.2%*	

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate

group vs. 1 patient (1.4%) in the unencapsulated group who had surgical resection performed after successful downstaging post-SBRT.

The 1-year and 2-year local control rates were better for encapsulated tumour (92.2 vs. 69.2%, 89.1 vs. 51.4%, respectively, $p < 0.001$). The median time to local failure for the encapsulated group was not yet reached versus 27.3 months (95% CI 16.9–37.6 months; Fig. 1a). In multivariate analysis, tumour capsule was an independent prognosticator of better local control (HR: 0.16, 95% CI 0.06–0.40, $p < 0.01$). Other independent positive prognostic factors included absence of vascular permeation and low AFP level (< 400 ng/ml; Table 2).

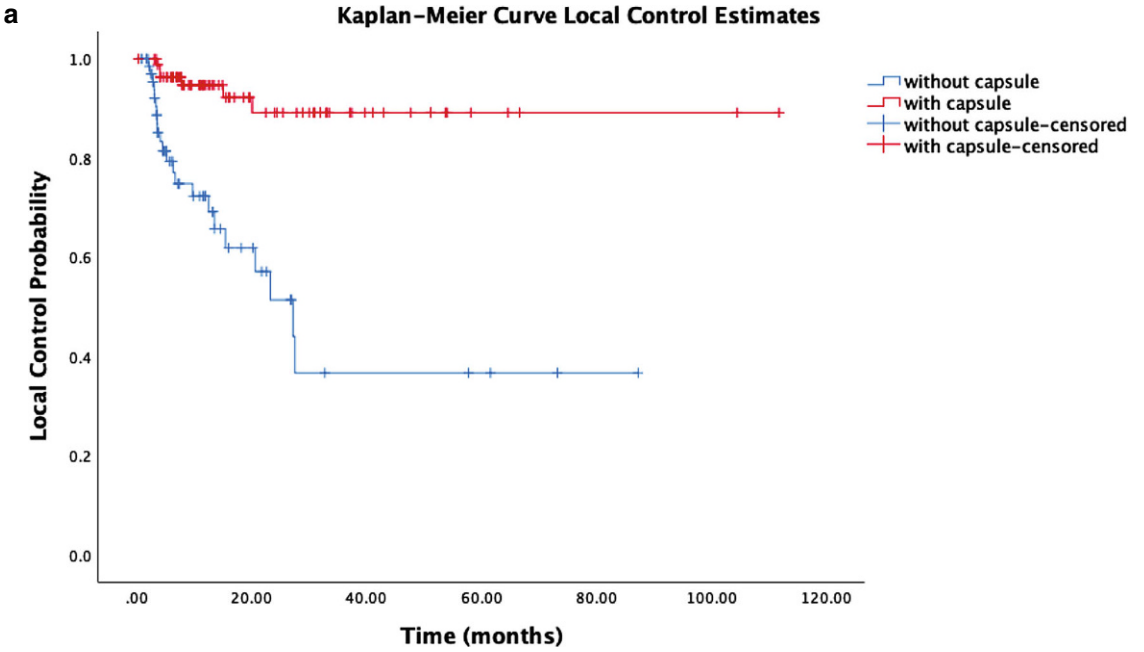
Discussion

SBRT has been increasingly used as a local treatment for patients with HCC over the past two decades, yet few studies have identified useful radiological markers for patient selection despite cross-sectional imaging being one of the most important assessment criteria for treatment allocation. To the best of our understanding, the present study is the first to recognize tumour capsule as a favourable prognostic marker in HCC patients undergoing SBRT. Our results showed that an intact tumour capsule is associated with superior local control, overall survival and objective response rate. This represents an opportunity for clinicians to select patients and tumours more likely to yield favourable SBRT outcomes. Although our prescribed dose of SBRT was insufficient to ablate large-sized tumours, previous literature and our experience have suggested that such a dose could provide clinically meaningful local control [7, 23, 24].

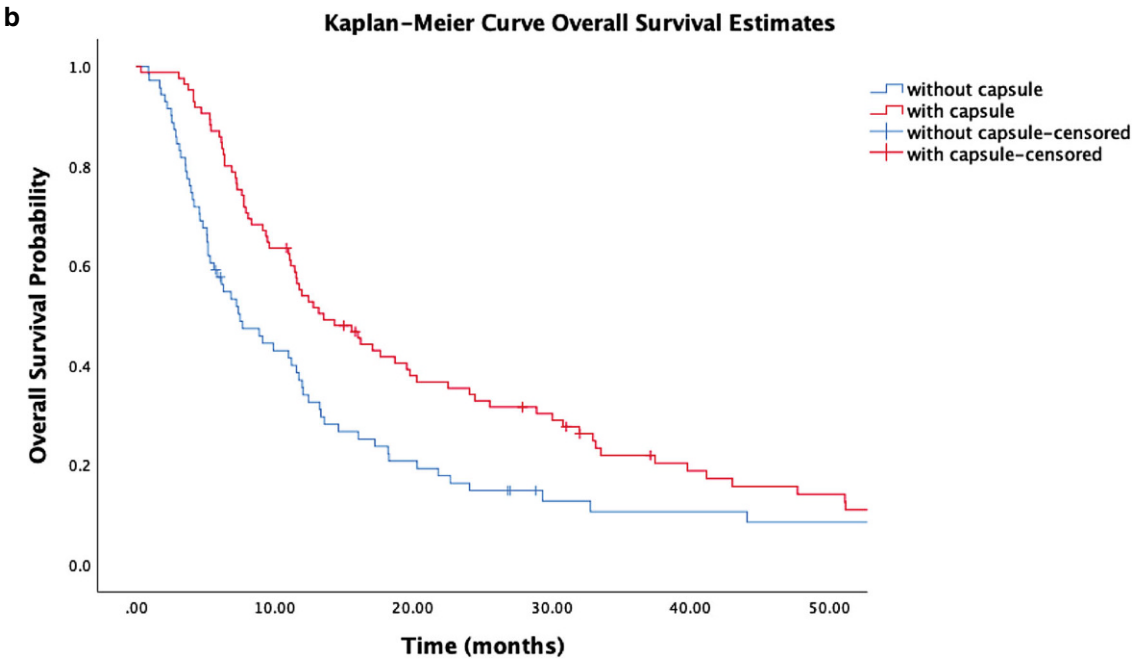
A myriad of clinical prognostic factors have previously been identified in patients with HCC undergoing SBRT: portal vein tumour thrombosis, Child–Pugh (CP) score > 7 and albumin-bilirubin (ALBI) score are known unfavourable prognosticators [25–27]. However, these clinical factors only provide patient-level prognostication, without taking into account tumour heterogeneity in multifocal disease in HCC [26]. In the era of precision medicine, where locoregional and/or systemic treatments are often used in combination to provide maximum therapeutic benefits [28, 29], lesion-level assessment is crucial. Our study is unique in providing a lesion-centric biomarker that not only serves as a survival prognosticator, but also potentially predicts the treatment response of SBRT. While promising, further randomized study is warranted to validate the role of capsule as an SBRT treatment response predictor.

Here, we have shown that the presence of a tumour capsule was associated with superior OS (1-year and 2-year: 53.9 vs. 35.5%, 34.1 vs. 14.8%, respectively, $p < 0.01$). This could be due to the significantly lower incidences of in-field (7.2 vs. 30.1%, $p < 0.01$) and out-field (54.2 vs. 60.3%, $p = 0.01$) failures in encapsulated tumours after SBRT. Perhaps this is not surprising given that the presence of a capsule is well known to be associated with a less aggressive HCC phenotype and a lower incidence of vascular permeation and microsatellite formation [11, 30]. Also, the presence of capsule may aid target volume delineation that accounts for the better in-field control. It is worth noting that large-sized HCCs (i.e. tumours > 5 cm) had a substantial intrinsic risk of vascular dissemination. Our results suggested that a capsule has a protective effect even in this high-risk group (median size of tumour in our cohort was 12.9 cm), reducing the chance of intrahepatic spread. However, we did not see any difference in the rates of distant metastasis or vascular invasion between the two groups, suggesting that different genetic and epigenetic mechanisms may be at play for extrahepatic spread of HCC. More in-depth radiogenomic understanding and radiologic/pathologic correlation would be necessary.

This study had several limitations. First, it is a retrospective study based on a database collected from a single institution with a relatively small sample size and heterogeneous patient population and treatment regimens. However, we included consecutive patients to minimise patient selection bias in our results. Second, we only concentrated on large-sized HCC in this study, and it remains to be seen whether our findings are applicable to smaller HCCs. Nevertheless, to the best of our knowledge, we are the first to investigate capsule prognosis in patients undergoing SBRT. Third, only CT images were used, which could affect the sensitivity and specificity of capsule detection [15]. To in-



	With capsule	Without capsule	*P*-value
Median, months (95% CI)	NA	27.3 (16.9-37.6)	$p<0.001$
1-year probability, % (95% CI)	92.2 (88.9-95.5)	69.2 (62.8-75.6)	
2-year probability, % (95% CI)	89.1 (84.7-93.5)	51.4 (42.5-60.3)	



	With capsule	Without capsule	*P*-value
Median, months (95% CI)	13.6 (9.2-17.9)	7.5 (4.6-10.4)	$p<0.01$
1-year probability, % (95% CI)	53.9 (48.7-59.0)	35.5 (30.0-41.0)	
2-year probability, % (95% CI)	34.1 (29.2-39.0)	14.8 (10.7-18.9)	

Fig. 1 Kaplan–Meier curves showing **a** local control and **b** overall survival (stratified by capsule status)

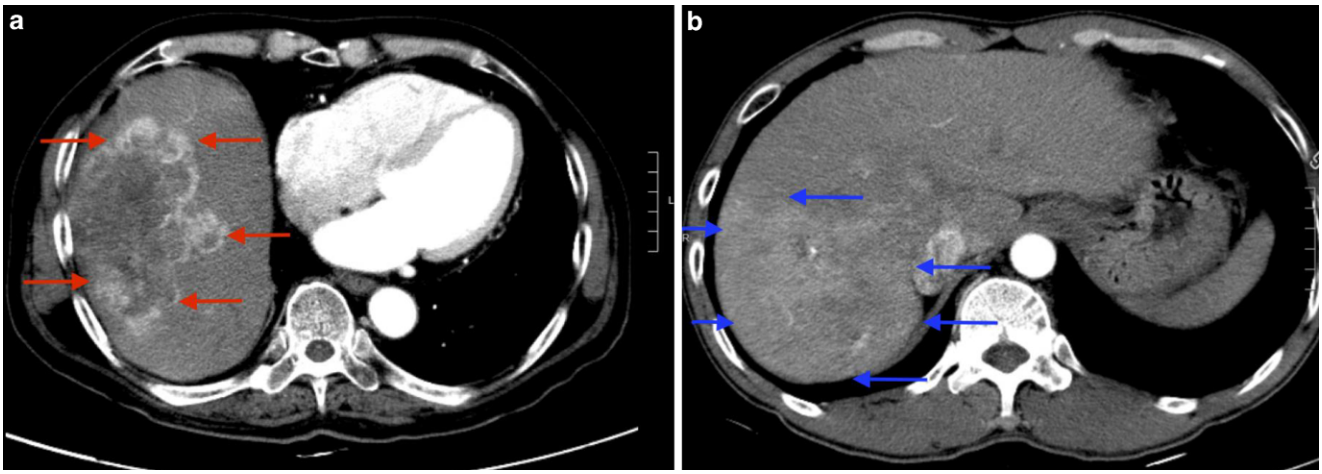


Fig. 2 Computed tomography images showing hepatocellular carcinoma (HCC) lesion with and without capsule. **a** M/84 with chronic hepatitis B presented with epigastric mass. Contrast-enhanced CT revealed a large discreet HCC with an intact capsule which is denoted by *red arrows*. **b** M/49 hepatitis B carrier referred from AED for abnormal liver function test and raised serum alpha fetoprotein. Contrast enhanced CT showed a large infiltrative HCC without a capsule. *Blue arrows* denote an ill-defined border

crease the objectivity and generalisability of our results, image analyses were performed in consensus by two experienced clinicians who are core members of the multidisciplinary team managing these patients. Nevertheless, the presence of a radiological tumour capsule may not necessarily equate to the presence of a histological capsule, as its appearances could be attributed either to a passive thickening of liver stroma under expansion pressure of the tumour or to a defence mechanism deployed by the surrounding parenchyma to restrain the tumour nodule that causes a mechanical insult to adjoining tissues [31]. The molecular basis of our findings warrants further investigations. Fourth, only the largest HCC nodule was referenced for capsule group allocation of patients with >1 intrahepatic lesions. However, SBRT only targets the most sizeable lesion for disease control, and this minimizes limitations in group assignment.

The implications of our findings may be beyond SBRT as a palliative treatment. In recent years, SBRT has been explored as a down-staging treatment in unresectable HCC. Our results suggest that tumour capsule may serve as a radiological biomarker in selecting eligible patients who are expected to have better tumour shrinkage and are less likely to experience out-of-field dissemination after radiation. Indeed, in our study, there was a substantially higher proportion of patients eligible for curative resection after tumour down-staging by SBRT (15.7 vs. 1.4%, $p<0.01$).

Conclusion

Our results have shown that tumour capsule is an independent prognostic marker in HCC patients treated with SBRT. Its presence was associated with improved local control, survival and tumour response. While a larger cohort is necessary to validate our results, consideration should be given to this radiological sign for treatment allocation and planning.

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Declarations

Conflict of interest S.H. Mak, S.M.N. Wong, W.H.K. Chiu, C.L. Chiang, W.L.W. Yip, H.M.C. Ho, S.Y.C. Yeung, K.H.M. Chan, W.Y.V. Lee and A.S.F. Lee declare that they have no competing interests.

Ethical standards *Ethics approval*: Institutional review board approval number: NTWC/CREC/18064. *Consent to participation and publication*: Need for patient consent was waived by the institutional review board.

References

1. Bosch FX, Ribes J, Díaz M, Cléries R (2004) Primary liver cancer: worldwide incidence and trends. Gastroenterology 127(5 Suppl 1):S5–S16. https://doi.org/10.1053/j.gastro.2004.09.011 (in eng)
2. Lafaro KJ, Demirjian AN, Pawlik TM (2015) Epidemiology of hepatocellular carcinoma. Surg Oncol Clin N Am 24(1):1–17. https://doi.org/10.1016/j.soc.2014.09.001 (in eng)
3. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM (2017) Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine 96(9):e5904. https://doi.org/10.1097/md.0000000000005904 (in eng)
4. Wahl DR et al (2016) Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol 34(5):452–459. https://doi.org/10.1200/jco.2015.61.4925 (in eng)
5. Su TS et al (2017) Long-term survival analysis of stereotactic ablative radiotherapy versus liver resection for small hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 98(3):639–646. https://doi.org/10.1016/j.ijrobp.2017.02.095 (in eng)
6. Shen PC et al (2019) Comparison of stereotactic body radiation therapy and transarterial chemoembolization for unresectable medium-sized hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 105(2):307–318. https://doi.org/10.1016/j.ijrobp.2019.05.066 (in eng)
7. Rim CH, Kim HJ, Seong J (2019) Clinical feasibility and efficacy of stereotactic body radiotherapy for hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. Radiother Oncol 131:135–144. https://doi.org/10.1016/j.radonc.2018.12.005 (in eng)
8. Shah S, Shukla A, Paunipagar B (2014) Radiological features of hepatocellular carcinoma. J Clin Exp Hepatol 4(Suppl 3):S63–S66. https://doi.org/10.1016/j.jceh.2014.06.009 (in eng)
9. Luca A et al (2010) Multidetector-row computed tomography (MDCT) for the diagnosis of hepatocellular carcinoma in cirrhotic candidates for liver transplantation: prevalence of radiological vascular patterns and histological correlation with liver explants. Eur Radiol 20(4):898–907. https://doi.org/10.1007/s00330-009-1622-0 (in eng)
10. Chernyak V et al (2018) Liver imaging reporting and data system (LI-RADS) version 2018: imaging of hepatocellular carcinoma in at-risk patients. Radiology 289(3):816–830. https://doi.org/10.1148/radiol.2018181494 (in eng)
11. Ng IO, Lai EC, Ng MM, Fan ST (1992) Tumor encapsulation in hepatocellular carcinoma. A pathologic study of 189 cases. Cancer 70(1):45–49. https://doi.org/10.1002/1097-0142(19920701)70:1 (in eng)
12. Xu X et al (2019) Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma. J Hepatol 70(6):1133–1144. https://doi.org/10.1016/j.jhep.2019.02.023 (in eng)
13. Lee CS, Hwang LY, Beasley RP, Hsu HC, Lee HS, Lin TY (1988) Prognostic significance of histologic findings in resected small hepatocellular carcinoma. Acta Chir Scand 154(3):199–203 (in eng)
14. Arnaoutakis DJ et al (2014) Recurrence patterns and prognostic factors in patients with hepatocellular carcinoma in noncirrhotic liver: a multi-institutional analysis. Ann Surg Oncol 21(1):147–154. https://doi.org/10.1245/s10434-013-3211-3 (in eng)
15. Tang A et al (2018) Evidence supporting LI-RADS major features for CT- and MR imaging-based diagnosis of hepatocellular carcinoma: a systematic review. Radiology 286(1):29–48. https://doi.org/10.1148/radiol.2017170554 (in eng)
16. Schwartz LH et al (2016) RECIST 1.1-Update and clarification: from the RECIST committee. Eur J Cancer 62:132–137. https://doi.org/10.1016/j.ejca.2016.03.081 (in eng)
17. Purysko AS, Remer EM, Coppa CP, Leão Filho HM, Thupili CR, Veniero JC (2012) LI-RADS: a case-based review of the new categorization of liver findings in patients with end-stage liver disease. Radiographics 32(7):1977–1995. https://doi.org/10.1148/rg.327125026 (in eng)
18. Grazioli L et al (1999) The pseudocapsule in hepatocellular carcinoma: correlation between dynamic MR imaging and pathology. Eur Radiol 9(1):62–67. https://doi.org/10.1007/s003300050629 (in eng)
19. Choi JY, Lee JM, Sirlin CB (2014) CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part II. extracellular agents, hepatobiliary agents, and ancillary imaging features. Radiology 273(1):30–50. https://doi.org/10.1148/radiol.14132362 (in eng)
20. Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30(1):52–60. https://doi.org/10.1055/s-0030-1247132 (in eng)
21. Wong VY, Tung SY, Ng AW, Li FA, Leung JO (2010) Real-time monitoring and control on deep inspiration breath-hold for lung cancer radiotherapy—combination of ABC and external marker tracking. Med Phys 37(9):4673–4683. https://doi.org/10.1118/1.3476463 (in eng)
22. Chiang CL et al (2019) Combined stereotactic body radiotherapy and trans-arterial chemoembolization as initial treatment in BCLC stage B-C hepatocellular carcinoma. Strahlenther Onkol 195(3):254–264. https://doi.org/10.1007/s00066-018-1391-2 (Kombinierte stereotaktische Körperstamm-Strahlentherapie und transarterielle Chemoembolisation als Erstlinientherapie beim hepatozellulären Karzinom im BCLC-Stadium B–C)
23. Bujold A et al (2013) Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 31(13):1631–1639. https://doi.org/10.1200/jco.2012.44.1659 (in eng)
24. Gkika E et al (2017) Excellent local control and tolerance profile after stereotactic body radiotherapy of advanced hepatocellular carcinoma. Radiat Oncol 12(1):116. https://doi.org/10.1186/s13014-017-0851-7
25. Que J et al (2016) Clinical outcomes and prognostic factors of cyberknife stereotactic body radiation therapy for unresectable hepatocellular carcinoma. BMC Cancer 16:451. https://doi.org/10.1186/s12885-016-2512-x (in eng)
26. Bibault JE et al (2013) Stereotactic body radiation therapy for hepatocellular carcinoma: prognostic factors of local control, overall survival, and toxicity. Plos One 8(e77472):10. https://doi.org/10.1371/journal.pone.0077472
27. Murray LJ et al (2018) Baseline Albumin-Bilirubin (ALBI) score in western patients with hepatocellular carcinoma treated with Stereotactic body radiation therapy (SBRT). Int J Radiat Oncol Biol Phys 101(4):900–909. https://doi.org/10.1016/j.ijrobp.2018.04.011 (in eng)
28. Kudo M et al (2020) Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 69(8):1492–1501. https://doi.org/10.1136/gutjnl-2019-318934 (in eng)
29. Assenat E et al (2019) Sorafenib alone vs. sorafenib plus GEMOX as 1(st)-line treatment for advanced HCC: the phase II randomised PRODIGE 10 trial. Br J Cancer 120(9):896–902. https://doi.org/10.1038/s41416-019-0443-4 (in eng)
30. Lim JH, Choi D, Park CK, Lee WJ, Lim HK (2006) Encapsulated hepatocellular carcinoma: CT-pathologic correlations. Eur Radiol 16(10):2326–2333. https://doi.org/10.1007/s00330-006-0203-8 (in eng)
31. Torimura T, Ueno T, Inuzuka S, Tanaka M, Abe H, Tanikawa K (1991) Mechanism of fibrous capsule formation surrounding hepatocellular carcinoma. Immunohistochemical study. Arch Pathol Lab Med 115(4):365–371 (in eng)