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Long term outcomes of Stereotactic Body Radiation Therapy (SBRT) for Hepatocellular Cancer (HCC) without Macrovascular Invasion

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Abstract

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AUTHORS' CONTRIBUTION

ASM, DO, TSL and LAD contributed to literature search, figures, study design, data collection, data analysis, data interpretation, writing, manuscript review and final approval. EGA contributed to figures, data analysis, data interpretation, writing and final approval of manuscript. CM contributed to data collection and data analysis. JR contributed to data generation, data interpretation, manuscript review and final approval. AB, JB, RD, JK, CC, RW, KC and MF contributed to data generation, manuscript review and final approval.

CONFLICTS OF INTEREST

LAD has a licensing agreement for Raysearch image registration software (unrelated). AB has a consulting/advisory role with Astra Zeneca. KC received research funding from BTG and Varian Medical Systems. MF has a consulting/advisory role in GenomeDx, Myriad Pharmaceuticals, NanoString Technologies and Varian Medical Systems. She receives honoraria from Medivation/Astellas (also in Speaker's bureau); Myriad Pharmaceuticals; Reflexion Medical and research funding from Celgene (I); Varian Medical Systems (Inst),She also received travel expenses from GenomeDx and has a pending patent for RadioType Dx, a biomarker test. ASM, EA, DO, RD, JK, JR, RW, CM, JB, CC and TSL had no conflicts of interest to declare.

Background: Stereotactic body radiotherapy (SBRT) is a non-invasive ablative treatment for hepatocellular carcinoma (HCC). This report aimed to address the limited availability of long-term outcomes post SBRT for HCC from North America.

Methods: Localized HCC patients without vascular invasion, who were ineligible for other liver-directed therapies and treated with SBRT at the University of Toronto or University of Michigan were pooled to determine overall survival (OS), cumulative recurrence rates, and ≥ grade 3 toxicity. Multivariable analysis determined factors affecting OS and local recurrence rates.

Results: In *297* patients with 436 HCCs (42% > 3 cm) one, three & five- year OS was 77·3%, 39·0%, and 24·1%, respectively. On Cox proportional hazards regression analysis, liver transplant post SBRT, Child Pugh (CP) A liver function, alpha-feto protein (AFP) ≤ 10 ng/ml , and Eastern Co-operative Oncology Group (ECOG) performance status 0 significantly improved OS.(hazard ratio {HR}=0·06, 95%CI- 0·02–0·25; *p<0·001*; {HR}=0·42, 95% CI-0·29–0·60, *p<0·001*; HR=0·61, 95% CI- 0·44–0·83; *p=0·002* and HR=0·71, 95% CI= 0·51–0·97, *p=0·034* respectively).

Cumulative—local recurrence was 6·3% (95% CI= 0.03–0.09) and 13·3% (95% CI=0.06–0.21) at one and three years respectively. Using Cox regression modelling, local control was significantly higher using breath-hold motion management and in HCC smaller than 3 cm (HR=0.52, 95% CI=0.58–0.98; *p=0.042* and HR=−0.53, 95%CI=0.26–0.98; *p=0.042*, respectively). Worsening of CP score by ≥2 points three months after SBRT was seen in 15·9%.

Conclusions: SBRT confers high local control and long-term survival in a substantial proportion of HCC patients unsuitable for, or refractory to standard local/regional treatments. Liver transplant should be considered if appropriate downsizing occurs following SBRT.

Keywords

Liver; cancer; hepatocellular carcinoma; stereotactic; radiation

INTRODUCTION

Curative treatments for hepatocellular carcinoma (HCC) include liver transplant, surgical resection, and local ablative therapies.[1] While transplant and surgical resection are associated with five-year survival rates of approximately 66%,[2] a minority of patients are eligible for liver transplant and resection is feasible only in patients with good liver function and sufficient liver remnant. Radiofrequency ablation (RFA) and microwave ablation are alternative local therapies for small HCCs; however, risk of recurrence increases as the HCC diameter increases above 3 cm, and some patients recur post local ablation or are not well-suited for ablative treatments due to tumor location, size, multifocality, impaired liver function and/or medical contraindications.[3] Transarterial chemo embolization (TACE) improves overall survival (OS) but is not curative[4] and is associated with an 80% recurrence rate over two years. Overall, a substantial proportion of patients are ineligible for, or recur following standard local-regional therapies, and thus have inherently worse prognosis.

SBRT is a non-invasive ablative treatment established as a curative treatment for lung cancer and for ablation of oligo-metastases from a variety of primary cancers.[5,6] For HCC, SBRT has generally been reserved for patients who are either high-risk, ineligible, or have

progressed despite other liver-directed therapies.[7] Several studies, majorly from Asia, have shown its potential role in all stages of HCC.[8] There are no published randomized trials comparing SBRT with other liver directed therapies. We report pooled long-term outcomes of patients with early, intermediate and advanced Barcelona Clinic Liver Cancer (BCLC) stage HCC, generally unsuitable for or refractory to standard local therapies, treated in two North American centres. We hypothesize that SBRT of HCC in patients ineligible for standard liver- directed therapies, or with recurrence following such therapies, would result in a high rate of durable long-term local control and a substantial proportion of patients alive three to five years post SBRT.

MATERIALS AND METHODS

Patients

This included HCC patients without vascular invasion, treated with SBRT at the Princess Margaret Cancer Centre (PM) and the University of Michigan (UM). Patients from UM were part of a prospectively maintained database, while data was retrieved retrospectively at PM. Eligibility criteria included patients with a histological or radiological diagnosis of T1, T2 or T3a HCC (AJCC TNM 7th edition) who were planned for SBRT from 1st June 2003 to 31st December 2016, and received biologically effective doses (BED) of at least 45 Gy_{10}, which is equivalent to 30Gy in six fractions, the lowest dose fractionation schedule used at PM as per the Phase I/II trial.[9] Exclusion criteria included vascular invasion, extrahepatic spread, ruptured HCC, ≥ five HCCs and patients who received planned systemic therapy after SBRT.[10,11] Tumors treated with SBRT as a bridging therapy to planned liver transplant and patients with no imaging or clinical follow up after treatment completion were also excluded (Fig 1). There was no upper limit to HCC size, and bland vascular thrombosis was permitted, as long as there was no definite HCC vascular invasion, as reviewed by an experienced hepatobiliary radiologist. Patients at both institutions were evaluated within a multi-disciplinary framework and generally deemed ineligible for other standard therapies due to co-morbidities or technical reasons, or as failure of prior therapies (e.g. RFA, TACE) before being offered SBRT.

Patient demographics, tumor characteristics and treatment details were retrieved from electronic medical records up to May 10, 2018. HCCs were labelled ‘recurrent’ if, at the time of irradiation, the target HCC had already recurred despite prior local-regional therapy of that lesion. Each session of prior liver-directed therapy was counted as one line of therapy.

Treatment

Treatment techniques mirrored the evolution of SBRT technologies from 2003 to 2016. Multiphasic contrast enhanced CT scans and MRI scans (when eligible), abdominal compression or breath hold {using “Active Breathing Coordinator” device (ABC™, Elekta, Stockholm, Sweden) or SDX® (Dyn’R, Toulouse, France)} motion management were used in majority of patients. Individualised dose allocation and daily image guidance were used for all patients. Details of SBRT were described in prior publications.[9,12,13]

Follow-Up

Follow-up was every three months for the first year, and every three/six months subsequently. Tumor response was assessed with multi-phasic CT or MRI hepatic imaging using RECIST 1·1 criteria[14]. Local recurrence was defined as progressive HCC (as per RECIST 1.1 criteria) within the irradiated volume. Laboratory parameters were collected at baseline and each follow-up visit. Toxicity was defined as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) V4.03;[15] with acute toxicity occurring < 90 days after SBRT. Radiation Induced Liver Disease (RILD) (both classic and non-classic) and change in ALBI score at three months after SBRT were also captured.

Statistics

Primary outcome, OS, was calculated using the Kaplan-Meier product-limit method, from the date of first fraction of SBRT to time to death or most recent follow up. Secondary outcomes included cumulative incidence of local recurrence, intrahepatic recurrence outside the irradiated volume, extrahepatic recurrence and progression-free survival (PFS). Cumulative incidence of local failure was calculated per lesion using Fine and Grey's competing event analysis method, considering death as competing event.[16] Univariate analysis of factors affecting OS and local recurrence was completed. Multivariable analysis was done using Cox proportional hazards model, including factors either potential $p\text{-}value < 0.20$ in the univariate analysis or deemed clinically important. Location of treatment (PM versus UM) was accounted for in the model. All P-values were two-sided, and $P < 0{\cdot}05$ was considered significant. Missing data was excluded and statistical analyses were performed using version 9.4 of the SAS system for Windows (2002–2012 SAS Institute, Inc., Cary, NC).

RESULTS

Patient and Tumor Characteristics

One hundred and ninety-nine patients were identified from UM, and 98 patients from PM, for a total of 297 HCC patients with 436 tumors (Table 1). Previous publications from UM and PMH describe less than half of the present cohort.[11–13.] With a median follow up of 19·9 months, 57.5% of patients expired at last follow up.

Patients were presented at a multidisciplinary HCC tumor board, where standard local and regional therapies were prioritized above SBRT. The cohort was heterogeneous in terms of tumor burden, liver function and performance status, as well as previous lines of treatment received (Table 1). Higher doses were used at UM compared to PM [median biologically effective dose (BED) = 85·5 Gy versus 64·4 Gy]. Twenty-three percent of patients (exclusively from UM) had a pre-planned break of a month after the third fraction of SBRT, as part of a clinical protocol,[12] and 8% had fiducials implanted to aid in image guidance. Although only six percent patients had T3aN0M0 disease, 53% patients were classified as BCLC Class C/D on the basis of ECOG PS > 0 and CP C. Twenty-five patients (8·4%) ultimately underwent a liver transplant following SBRT. At PM, no patients who underwent SBRT as a bridge to transplant or who were planned to receive a liver transplant were included a priori. Despite this exclusion, five patients unexpectedly became eligible for

transplant due to substantial reduction in HCC volume post SBRT. At UM, patients were not identified as eligible for transplant upfront; 20 patients subsequently went on to have a liver transplant following downsizing post SBRT.

Overall Survival

Median OS of this heterogeneous cohort, mostly ineligible for other liver-directed therapies was 25·6 months (95% CI=22·3–31·7) with one, three and five- year survival rates of 77·4%, 39·0% and 24·1% respectively. Patients with better performance status and liver function (ECOG PS 0 and CP A) had a median OS of 37 months (95% CI=25–51), compared to 23 months (95% CI= 19–24) for those with ECOG PS ≥1 and/or CP B/C. On multivariable analysis, liver transplant post SBRT, CP A liver function, AFP ≤10, and ECOG PS 0 were significantly associated with improved OS (Table 2). Median OS of those who underwent liver transplant after SBRT has not been reached, and it was 24 months (95% CI=20·5–27·2) in patients who did not undergo transplant (Figure 1). Patients with CP A had a median OS of 31·7 months (95% CI=24·0–38·5) compared to a median of 23·2 months (95% CI=18·8–28·0) for CP B or C patients. Those with AFP ≤10 had a median OS of 32·9 months (95% CI=24·9–47·2) vs 21·1 months (95% CI=17·0–25·7) for those with AFP >10. Median survival of patients with tumors larger than five cm was 28 months (95% CI=20.0–38·0), not significantly different from those with smaller tumors (median OS= 26·0 months; 95% CI=22·0–32·0). In addition, in analysis of subgroups, BCLC B patients (more than three tumors or at least 1 tumor>3cm), with ECOG PS 0 and Child Pugh A liver function had a 3 year OS of 54.6%. Calendar period was not found to be significant on univariate analysis. On multivariable analysis, there was no significant effect of treating center on OS.

Local Control and other Progression

Cumulative incidence of local HCC recurrence (i.e. RECIST progression of the irradiated HCC's) was 6·3% (95% CI= 0.03–0.09) at one year and 13·7% (95% CI=0.04–0.23) at five years (Fig 3). On univariable analysis, HCC size < 3cm, higher dose, use of fiducial markers for image guidance and breath-hold immobilization had a lower likelihood of local recurrence (Table 2). Use of fiducial markers was excluded from multivariable analysis as number of events were too small. Tumor size and prescribed dose were significantly correlated with each other. When prescribed dose was excluded from the multivariable model, breath hold motion management and HCC size <3 cm were both significantly associated with improved local control (Table 2). This exploratory analysis needs validation due to few events. Only 3·7% of patients had isolated recurrence of the irradiated HCC as the first site of recurrence. The number of patients alive with no progression at 1 and 3 years is 131 and 28 respectively, and the number of patients alive with no local recurrence at 1 and 3 years is 261 and 72 respectively.

Rates of intrahepatic recurrence/new HCC outside the irradiated HCC were higher: 31·2% and 65·7% respectively at one and five years. Cumulative rates of extrahepatic recurrence were 16·6% at 1 year and 29·3% at five years. Median PFS was 10·6 months (95% CI=8·9–12·3) with 14.9% (95% CI=10.7%−19.6%) patients alive and progression-free three years post SBRT (Fig 3).

Toxicity

Low rates of clinical toxicity were observed; 15.9% out of 214 evaluable patients experienced a worsening CP score and 21·2% of 241 evaluable patients had a worsening in ALBI grade, three months after SBRT (Table 3). No patients developed classic RILD or Grade 4 liver enzyme toxicity. Two patients who had undergone prior therapies (TACE, RFA, Y^{90} radioembolization and a biliary-enteric anastomosis), and a third patient with a tumor adjacent to the biliary duct, developed biliary toxicity at one, one-and-a-half and 30 months post SBRT, respectively. One patient possibly succumbed to late toxicity from a duodenal ulcer and an upper gastrointestinal bleed, 10 months post SBRT.

DISCUSSION

This pooled North American analysis of 297 HCC patients without macrovascular invasion showed that SBRT was well tolerated and demonstrates long-term tumor control in the majority of patients. Despite the inclusion of patients with large tumors and those ineligible for, or with recurrence following standard local-regional therapies, who are typically excluded from other series, the median overall survival was 31·7 and 23·2 months for CP A and CP B/C patients, respectively. In addition to baseline CP A liver function, survival was best in patients with a better performance status, lower AFP levels and in those who went on to receive a transplant. Local recurrence of the irradiated HCCs was low (3·7% as isolated first recurrence and 13% at three years), and there was no significant dose effect, emphasizing the radiation responsiveness of HCC to SBRT. Thus, SBRT is a non-invasive ablative treatment with a high chance of long-term control even in HCC patients who are ineligible for other liver-directed therapies. Most reports of HCC treated with hepatic resection (five year OS 66·5% to 79·3%) or RFA (five year OS 49·8% to 67·4%) include only patients with no or minimal medical comorbidities, with CP A liver function, and limited tumor burden.[17] In contrast, 40% of our patients received SBRT for recurrent HCC after other ablative or regional therapies, 30% had multifocal lesions, 42% were > 3cm, 54% were symptomatic with a reduced performance status (ECOG ≥1) and 22% had CP B or C liver function. Patients in the present cohort are higher risk than patients in series of other ablative therapies, including radiation series from Asia which tend to include earlier stage HCC and planned TACE prior to SBRT. These series report three-year OS from 53·8% to 73·5%[8,11–13, 18–20] following photon RT and five-year OS and LC rates of 25–38·7% and 81–92·8% respectively following proton therapy.[21–22] In spite of poor prognostic factors in the present cohort, SBRT controlled majority of tumors and conferred long-term survival in almost a quarter.

At three years, our local recurrence rate of 13·7% was slightly higher than the series by Takeda et al and Sanuki et al, that reported 90%−91% three-year local control.[19,20] This may in part be due to the differences in patient populations cited earlier, and since competing risks were taken into account in the present study. Use of fiducial markers to aid in image guidance and breath-hold immobilization (surrogates for higher SBRT precision and accuracy) were associated with trends for improved local control. Local control was slightly lower in tumors larger than 3 cm compared to those less than 3cm,, but there was no worsening of local control for tumors larger than 5 cm. Despite the inclusion of large

tumors, durable local control was observed in the majority of the patients, with three-year local control rates of 90% (95% CI: 81%−99%) and 80% (95% CI: 67%−93%) in HCCs ≤ 3cm and > 3 cm (up to 18 cm) respectively. The study results are not easily comparable to series of RFA or other interventions, since the patients included herein were generally ineligible for or had progressive despite prior loco-regional therapies; with this caveat, our results appear to be similar to series of RFA and/or TACE used to treat similar patients.[23,24] For SBRT, effectiveness and safety are related to the volume of liver that can be spared and proximity of HCC to luminal gastrointestinal tissues.

Despite the low median biologic doses used, the wide range of doses used in this cohort, and the range of tumor sizes, local control rates are high, and prescribed dose to the tumor did not significantly affect the local control rates, at least at the time points studied, i.e. two to three years. This adds to the literature supporting the view that HCC is sensitive to moderate doses of radiation. However it is possible that with longer follow up, a dose-response may be observed. Delayed local recurrence beyond 1 year was seen in a minority of patients, providing rationale for continued imaging surveillance for these patients.

SBRT was associated with low toxicity. Only 1·3% of patients experienced ≥ grade 3 gastrointestinal (GI) luminal toxicity (gastric/duodenal ulcers, gastritis or upper GI bleed). Three patients (with either prior biliary enteric anastomoses or Y90), developed biliary toxicity. SBRT should be used with caution in such patients and given the lack of dose effect on local control, lower doses are preferred when treating central HCCs adjacent to the biliary tract. Classic RILD was not observed. The dose constraints to the critical organs-at-risk (normal liver, stomach, duodenum, large and small bowel) that were adopted in this study, as reported in prior publications[9] and being the basis of the ongoing trials,[10] seem to show continuing safety for routine clinical use. Baseline CP score B or C was associated with an increased risk of decline in liver function post SBRT.[25,26] Interestingly, El Naqa et al found that approximately 10% of HCC patients who did not receive any therapy had a worsening of CP score at 3 months.[27] Novel approaches to mitigate declining liver function and to reduce the risk of toxicity post SBRT are needed, especially in patients with impaired liver function.

Patients with poor liver function are best served with a liver transplant. In such patients, there is rationale for offering SBRT as a strategy to downsize and perhaps convert previously ineligible HCC patients (due to excessive volume) to become suitable for potential liver transplant. Not surprisingly, patients who received transplant post SBRT had far better survival then those who did not, adding to the growing body of evidence that SBRT, which is also non-invasive, may be used to bridge or downsize HCC to acceptable criteria for transplant.[28]

The predominant pattern of intrahepatic recurrence, inherent to patients with cirrhosis and multifocal and/or recurrent HCC, provides a compelling rationale for investigating combined modality treatment in high risk patients. To this end, TACE is being investigated in clinical trials in combination with SBRT,[29] as are sorafenib[9] and other systemic therapies.[30]

Emerging paradigms for combined modality therapy include the use of immunotherapy in advanced unresectable HCC patients. PD-1 checkpoint inhibitors, and more recently the combination of the PD-L1 inhibitor atezolizumab and the VEGF-inhibitor bevacizumab have shown effectiveness in HCC patients.[31] Several case series have reported the elusive abscopal effect i.e. response of unirradiated metastases when the primary HCC is irradiated, [32]; preclinical work suggests that hypofractionated radiation is more immunogenic than conventional radiation therapy.[33]The combination of immunotherapy and radiation therapy has high promise to improve the therapeutic ratio in future HCC patients, and is an area of active investigation.[34]

A limitation of this study is that it is retrospective, with a heterogeneous high-risk HCC population, although the majority of patients from UM were from a prospective database. Also, RECIST 1.1, which was used for response assessment, is known limited. Studies of biomarkers and more objective strategies for monitoring response are needed not only following SBRT, but also following other HCC treatments.

CONCLUSION

In summary, this large North American series demonstrated that SBRT is a safe and effective option for high risk HCC patients unsuitable for or refractory to standard local treatment options. SBRT is associated with a high likelihood of sustained local HCC control, but the majority of patients develop progression or new HCCs outside the irradiated volume, providing rationale for combined modality studies in high-risk patients. Patients with CP B & C liver function are at increased risk of developing liver toxicity, and liver transplant should be considered in these patients if downsizing occurs following SBRT.

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HIGHLIGHTS

- Stereotactic radiation provides durable tumor control in early hepatocellular cancer
- Patients unsuitable or refractory to other local therapies too had good outcomes
- Good liver function and performance status at baseline predicted for better survival
- Down staged tumors may be considered for liver transplant which improves survival

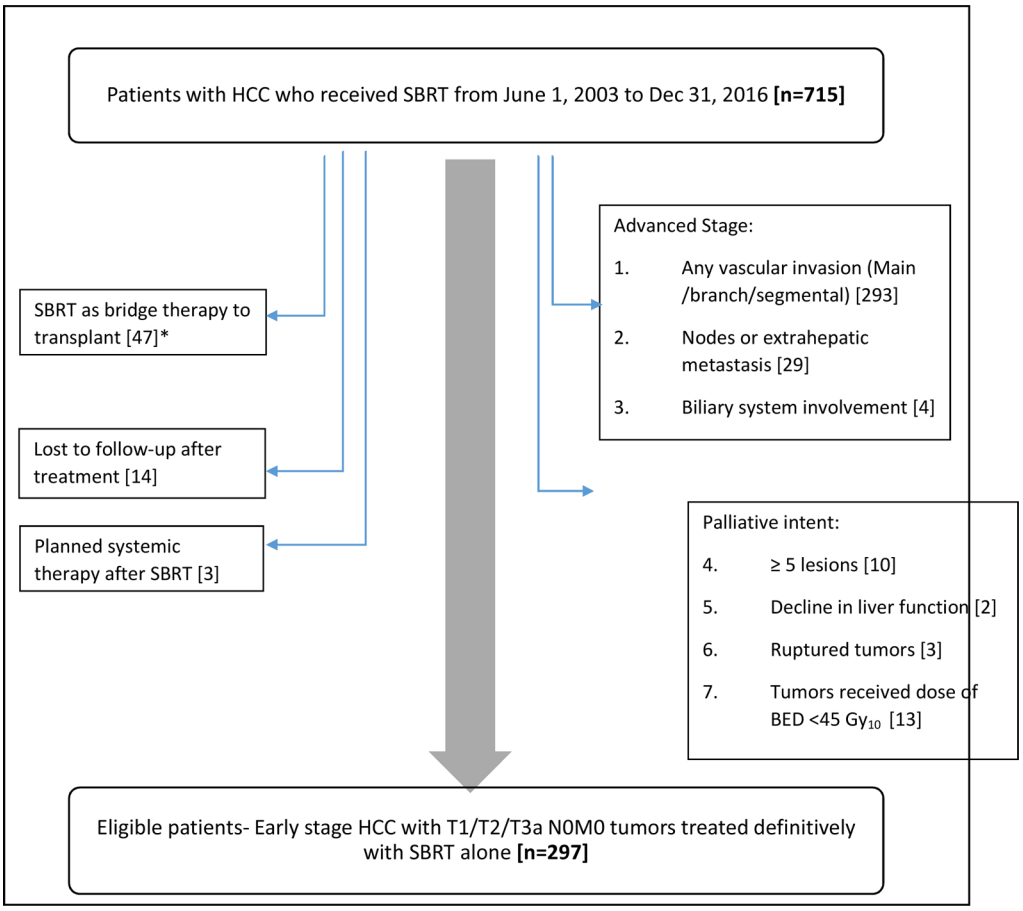

Figure 1. CONSORT Diagram.

HCC- Hepatocellular carcinoma; SBRT- Stereotactic Body Radiotherapy; *At Princess Margaret Cancer Centre, patients who underwent planned SBRT as a bridge to transplant received SBRT to reduce the tumor burden to within transplant criteria, rather than for definitive treatment (and often all HCCs were not always targeted and SBRT doses were often reduced); hence they were excluded from this analysis. At University of Michigan, no patients were identified as eligible for transplant upfront. However, a subset of patients subsequently became eligible for transplant, and are included in this analysis.

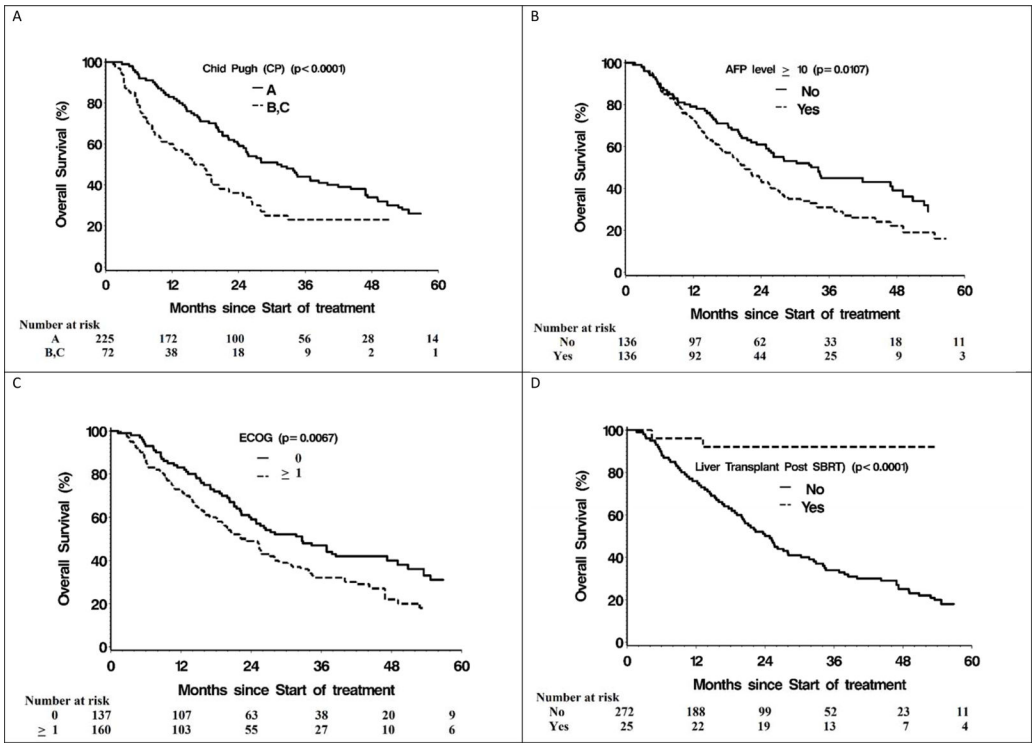

Fig 2.

Overall Survival stratified by (A)Chid Pugh (CP) score, (B) Alpha-fetoprotein (AFP) level, (C) Eastern Co-operative Group (ECOG) Performance Score and (D) liver transplant post SBRT or not. CP- Child Pugh classification; ECOG- Eastern Co-operative Oncology Group; AFP- alpha-fetoprotein

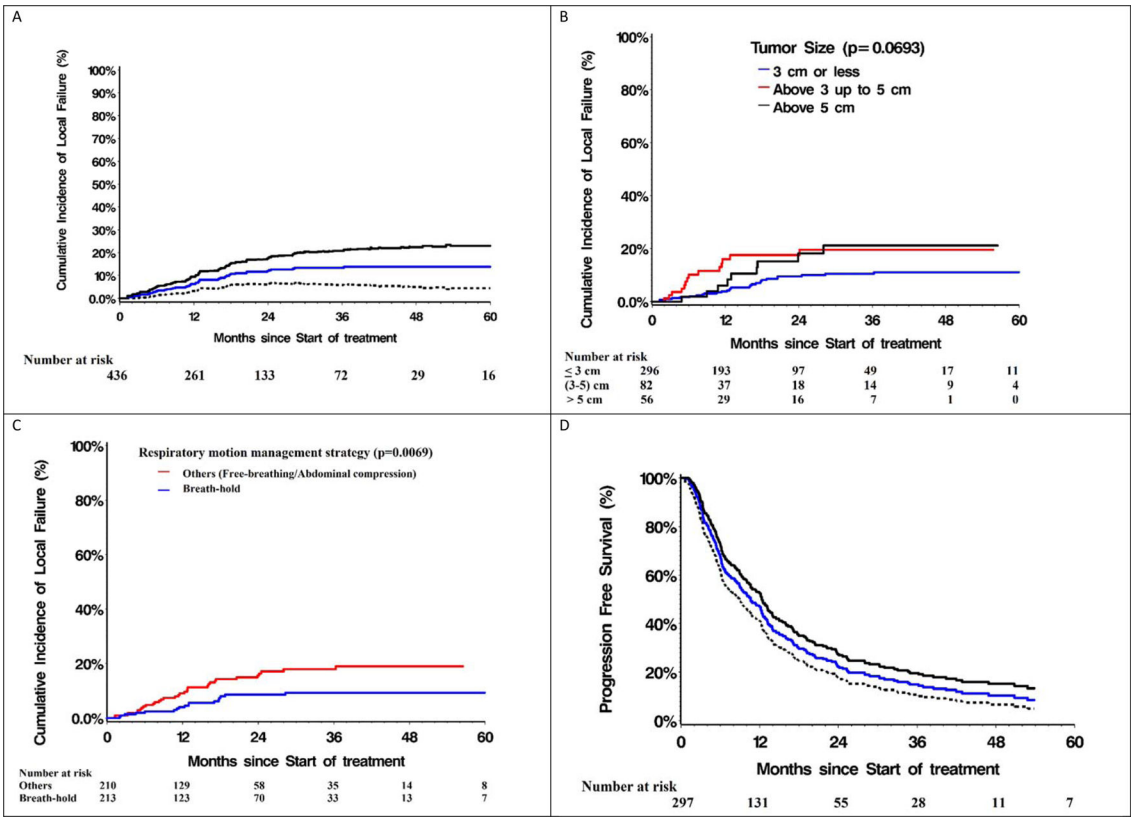

Figure 3.

(A) Cumulative incidence of local recurrence of full cohort (with ± 95% confidence intervals) and stratified as per (B) tumor size (≤3cm, >3 cm-≤5cm and >5cm), and (C) respiratory motion management strategy (Breath hold techniques and Other techniques). (D) Progression-free survival (PFS) of full cohort (with ±95% confidence intervals).

Table 1.

Patient Demographics and Treatment Characteristics

Factor	Description	Princess Margaret Cancer Centre (%) N=98	University of Michigan (%) N=199	Combined Cohort (%) N=297
Age at treatment	Median (Range)	76 (39–94)	64.5 (22–90)	69.3 (22–94)
Sex	Male/ Female (%)	70/28 (71/29)	151/48(76/24)	221/76 (74/26)
Ethnicity (%)	Caucasian	52 (53)	154 (77)	206 (69)
	Asian	39 (40)	8 (4)	47 (16)
	African-American	1 (1)	19 (10)	20 (7)
	Other	6 (6)	18 (9)	24 (8)
ECOG Score	0 (%)	48 (49)	88 (44)	136 (46)
	≥1 (%)	50 (51)	111 (56)	161 (54)
Cirrhosis	Yes	80 (82)	176 (88)	256 (86)
Aetiology of Cirrhosis	Hepatitis C	20 (20)	100 (50)	120 (40)
	Hepatitis B	23 (23)	14 (7)	37 (12)
	Non-viral	37 (38)	63 (32)	100 (34)
	None	18 (18)	22 (11)	40 (14)
Child-Pugh Class	**A 5**	67 (68)	86 (43)	153 (52)
	A 6	20 (20)	52 (26)	72 (24)
	B 7	7 (7)	17 (9)	24 (8)
	B 8	1 (1)	19 (10)	20 (7)
	B 9	0 (0)	15 (8)	15 (5)
	C ≥ 10	0 (0)	6 (3)	6 (2)
	Missing	3 (3)	4 (2)	7 (2)
ALBI Score	Median (Range)	−2.43 (−3.27 to −0.92)	−2.26 (−3.33 to −0.49)	−2.33 (−3.33 to −0.49)
	IQR	−2.71 to −2.13	−2.68 to −1.72	−2.69 to −1.91
ALBI Grade[a]	Grade 1	36 (37)	57 (29)	93 (31.3)
	Grade 2	58 (59)	118 (59)	176 (59.3)
	Grade 3	4 (4)	23 (11.6)	27 (9)
	Missing	0	1 (0.5)	1 (0.3)
Pre-treatment Platelets (X 10^9/L)	Median (Range)	135 (34–366)	100 (17–476)	111 (17–476)
Time since original diagnosis of HCC (months)	Median (range)	9.4 (1–209)	8.6 (1–116)	9 (1–209)
No of Liver Occurrences prior to SBRT	Median (range)	0 (0–10)	0 (0–6)	0 (0–10)
Liver directed Therapies prior to SBRT	Yes (%)	48 (50)	130 (65)	178 (60)
	Median no. of lines (range)	0 (0–18)	1 (0–7)	1 (0–18)
	Types of therapies			
	TACE	20 (15)	178 (60)	198 (46)
	RFA/MWA	82 (60)	79 (26)	161 (37)
	Resection	9 (7)	26 (9)	35 (8)

Factor	Description	Princess Margaret Cancer Centre (%) N=98	University of Michigan (%) N=199	Combined Cohort (%) N=297
	Miscellaneous[b]	25 (18)	16 (5)	41 (9)
T stage as per AJCC/UICC[c]	T1	52 (53)	149 (75)	201 (68)
	T2	30 (31)	48 (24)	78 (26)
	T3a	16 (16)	2 (1)	18 (6)
BCLC Classification	Class 0/A (Early)	16 (16)	64 (32)	80 (27)
	Class B (Intermediate)	31 (32)	21 (11)	52 (18)
	Class C[d]/D (Advanced)	48 (49)	110 (55)	158 (53)
	Not Available	3 (3)	4 (2)	7 (2)
Number of lesions per patient (%)	1	60 (61)	149 (75)	209 (70.4)
	2–3	33 (34)	48 (24)	81 (27.3)
	4	5 (5)	2 (1)	7 (2.4)
Tumor size (cm)	Median (range)	4.4 (1.2–18.1)	2.3 (0.5–13.4)	2.7 (0.5–18.1)
Tumor size category (%)	≤ 2 cm	14 (14)	87 (44)	101 (34)
	2 to ≤ 3cm	18 (18)	54 (27)	72 (24)
	3 to ≤ 5 cm	26 (27)	43 (22)	69 (23)
	> 5 cm	40 (41)	15 (8)	55 (19)
Pre-treatment AFP (ng/mL)	Median (range)	9.5 (0–14472)	9.7 (0–10926)	9.7 (0–14472)
GTV volume (cc)	Median (range)	53.2 (1.3–2519.1)	10.3 (0.8–1108.6)	15.6 (0.8–2519.1)
PTV volume (cc)	Median (range)	141.8 (10–3091.6)	42.7 (1.6–1607.4)	56 (1.6–3091.6)
Prescribed Dose (Gy)	Median (range)	39 (30–54)	42 (27–60)	40 (27–60)
Prescribed number of fractions	Median (range)	6 (5–6)	5 (3–5)	5 (3–6)
BED (Gy)[e]	Median (range)	64.4 (45–102.6)	85.5 (51.3–180.0)	79.2 (45–180)
Respiratory Motion management per lesion (N=436) (%)	Breath hold[f]	41 (28)	169 (58.3)	210 (48)
	Abdominal Compression	94 (64)	0 (0)	94 (22)
	Free-breathing	11 (8)	108 (37.2)	119 (27)
	Not available	0 (0)	13 (4.5)	13 (3)
Fiducials (N=436) (%)	No	146 (100)	255 (88)	426 (92)
	Yes	0 (0)	35 (12)	37 (8)

NAFLD- Non-Alcoholic Fatty Liver Disease; ECOG score- Eastern Co-operative Oncology Group performance status score; ALBI score-

Albumin Bilirubin score, RFA- radio frequency ablation; MWA- microwave ablation; TACE-trans arterial chemoembolization; BCLC- Barcelona Clinic Liver Cancer Classification, AFP- alpha-fetoprotein, GTV- gross tumor volume; PTV- planning target volume.

[a] ALBI Grade 1= ≤ −2.6; Grade 2= >−2.6 to ≤−1.39; Grade 3=>−1.39

[b] Miscellaneous liver directed therapies included- Percutaneous ethanol ablation, Irreversible electroporation, Y^{90} Radioembolization or any combination of these. Each session of ablation/TACE was counted separately.

[c] UICC/ AJCC 7th Edition, 2010

[d] BCLC C- on basis of performance score 1 or 2

[e] BED- Biologically Effective Dose= nd {1+ d/(α/β)} where n=number of fractions, d= dose per fraction in Gy and α/β=10)

[f] Breath hold with active breath control (ABC) or spirometric motion management system, SDX® (Dyn'R, Toulouse, France)

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Table 2.

Univariable and Multivariable Analysis for factors affecting Overall Survival and Local Progression

Variable	Category[a]	Overall Survival				Local Progression			
		Univariate analysis		Multivariable Analysis		Univariate analysis		Multivariable Analysis	
		HR (95% CI)	p-value[b]	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Transplant post SBRT	Yes vs No	0.08 (0.02–0.31)	**0.0003**	**0.06 (0.02–0.25)**	**<0.0001**	-	-	-	-
Pre-treatment CP score	A vs B,C	0.50 (0.36–0.70)	**<0.0001**	**0.42 (0.29–0.60)**	**<0.0001**	-	-	-	-
AFP	≤10 (median)vs >10	0.67 (0.49–0.91)	**0.0112**	**0.61 (0.44–0.83)**	**0.0020**	-	-	-	-
ECOG	0 vs ≥1	0.66 (0.48–0.89)	**0.0070**	**0.71 (0.51–0.97)**	**0.0339**	-	-	-	-
Cirrhosis	Yes vs No	1.69 (1.03–2.80)	**0.0398**			0.83 (0.40–1.74)	0.6233	-	-
Etiology of cirrhosis (ref=None)	HBV	1.01 (0.53–1.93)	**0.0441**	NS	NS	2.05 (0.93–4.48)	0.1601	-	-
	HCV	1.57 (0.93–2.63)				1.00 (0.49–2.01)		-	-
	Non-viral	1.80 (1.07–3.05)				1.60 (0.69–3.71)		-	-
Pre-treatment ALBI	Grade 1 vs Grade 2/3	0.75 (0.54–1.05)	**0.0897**	*d*	-	-	-	-	-
Age	>70 vs < 70 yrs.	0.78 (0.58–1.06)	0.1121	-	-	-	-	-	-
T-stage	T1 vs T2/3a	0.79 (0.57–1.09)	0.1451	-	-	0.98 (0.57–1.67)	0.9388	-	-
Decline in CP score	≥ 2 points vs <2 points	1.79 (1.15–2.77)	**0.0093**	*e*	-	-	-	-	-
No of tumors	1 (ref)	1.26 (0.91–1.75)	0.3363	-	-	Ref	0.7451	-	-
	2–3	0.78 (0.25–2.46)				1.10 (0.63–1.91)		-	-
	4					0.67 (0.19–2.43)		-	-
Prior Liver directed therapy	Yes vs No	1.06 (0.78–1.45)	0.7152	-		2.08 (0.50–8.64)	0.3147	-	-
Tumor size	≤ 3 cm vs >3 cm	0.96 (0.71–1.31)	0.8143	-		**0.53 (0.31–0.91)**	**0.0212**	**0.53 (0.29–0.98**	**0.0423**
	≤ 5 cm or >5 cm	0.94 (0.64–1.40)	0.7725	-		0.67 (0.33–1.36)	0.2674	-	-
Time since diagnosis of HCC	< 9 months vs>9 months	0.98 (0.72–1.32)	0.8669	-		-	-	-	-
Local progression	Yes vs No	0.95 (0.63–1.42)	0.7953	-		-	-	-	-
Fiducials	Yes vs No	-	-	-		0.00	**<0.0001**	*e*	
Respiratory motion management	Breath hold vs. compression/free breathing	-	-	-		**0.47 (0.26–0.84)**	**0.0106**	**0.52 (0.28–0.98)**	**0.0441**
Total SBRT physical dose		-	-	*f*		**0.96 (0.93–0.99)**	**0.0244**	-	-

Variable	Category[a]	Overall Survival				Local Progression			
		Univariate analysis		Multivariable Analysis		Univariate analysis		Multivariable Analysis	
		HR (95% CI)	p-value[b]	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Total GTV		-	-	-		1 (0.999–1.001)	0.4592	-	-

[a] Reference category is the latter category in each variable.

[b] Bold values indicate statistical significance.

[c] As pre-treatment ALBI was correlated with pre-treatment CP score, hence ALBI was not included in the model

[d] Was not included in the model as was correlated to Pre-treatment CP score

[e] Not included in the model as there were too few events

[f] Prescribed dose was not included in multivariable analysis for overall survival due to the inherent bias in dose allocation due to differing dose allocation strategies at both the participating institutions

Table 3.

Toxicity ≥ Grade 3 (CTCAE V 4.0) in Total Cohort

Toxicity	Grade 3	Grade 4	Grade 5	Grade 3, 4 or 5 Total (N=297)
Biochemical				73[a] (24.6%)
Bilirubin	35 (11.8%)	4 (1.3%)	0	
AST/ALT	41 (13.8%)	0	0	
ALP	2(0.6%)	0	0	
Gastrointestinal				
Biliary	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (1.0%)
Luminal GI toxicity	3 (1.0%)	0	1 (0.3%)	4 (1.3%)
Liver				
Ascites	23 (7.7%)	0	0	23 (7.7%)
Classic RILD				0 (0%)
CP score decline ≥ 2 at 3 months after SBRT				34 (15.9%)
ALBI Grade increase at 3 months after SBRT				51 (21.2%)

Toxicity reported includes acute and late toxicity at least possibly attributable to SBRT.

[a]Some patients had more than one kind of biochemical toxicity.