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Original Research Article

Do We Have a Winner? Advocating for SBRT in HCC Management

Amir H. Safavi [a], Laura A. Dawson [a,b,1], Aruz Mesci [a,b,*,1]

[a] Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada
[b] Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

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"Yesterday's home runs don't win today's games"
Babe Ruth (attributed)

Stereotactic body radiotherapy (SBRT) is a safe and effective locoregional therapy for inoperable patients with localized or recurrent hepatocellular carcinoma (HCC) and may be used as bridging therapy ahead of liver transplantation [1]. Compared to radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radioembolization (TARE), SBRT uniquely allows for risk-adapted prescription of ablative dosing to the entire tumor target across a range of tumor sizes and peritumoral vascularity. Recent clinical practice guidelines offer variable endorsement of SBRT as a standard-of-care treatment option for HCC. These range from recommended use of SBRT by the American Association for the Study of Liver Diseases (AASLD) and the American Society for Radiation Oncology (ASTRO) to omission of radiotherapy by the Barcelona Clinic Liver Cancer (BCLC) group [2–5]. How can we advocate for SBRT to be duly considered in day-by-day, multidisciplinary HCC management?

Yesterday's Home Runs Re-examined

We can highlight the lessons learned from recent comparative studies to promote SBRT as an ideal locoregional therapy for unresectable HCC (Table 1). Features of an ideal locoregional therapy include excellent local control, survival benefit, minimized morbidity, and cost-effectiveness (Table 2).

Local control

SBRT appears to provide superior and more durable local control (LC) when compared to TACE. LC is approximately 2–4 times higher following SBRT in a number of recent retrospective and prospective studies. Significantly superior LC rates ($p < 0.001$) were reported with SBRT at 1-year (97 % versus 47 %) and 2-years (91 % versus 23 %) in a propensity score analysis of a retrospective single-institution cohort with 1–2 unresectable HCC tumors (n = 209 patients [125 post-SBRT, 84 post-TACE], Child-Pugh [CP]-AB) [6]. In this study, macrovascular invasion (MVI) was associated with worse LC following TACE (HR 9.9, $p < 0.001$). Two prospective randomized controlled trials (RCT) have been published comparing TACE and SBRT [7,8]; both were closed early, one due to slow accrual and the other meeting pre-specified endpoints early, underscoring the challenge of generating high-quality comparative evidence with large sample sizes. SBRT was associated with superior LC (HR 0.15 [95 % CI, 0.04–0.4], $p = 0.0002$), corresponding to almost four times higher 1-year LC (84 % vs 23 %), in a single-center phase 3 trial of SBRT versus a second course of TACE (21 %) or bland embolization (79 %) (n = 40 patients, BCLC-AB, CP-AB) [7]. While accrual was slow, this trial was closed early when the threshold number of events was reached. In the poorly accrued TRENDY trial, a multi-center phase 2 RCT among patients ineligible for further surgery and RFA (n = 28, CP-A, one tumor per patient), time to local recurrence was longer following SBRT versus TACE (>40 months versus 12.0 months, HR 0.15 [95 % CI, 0.02–1.21], $p = 0.075$) [8]. On post-hoc per-protocol analysis of TRENDY, SBRT had

* Corresponding author at: Princess Margaret Cancer Centre, 610 University Ave, Toronto, Ontario M5G 2M9, Canada.
E-mail address: aruz.mesci@uhn.ca (A. Mesci).
[1] Co-senior authors.

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Table 1
Lessons learned from recent comparative studies of stereotactic body radiotherapy and other locoregional therapies for unresectable HCC.

LC	Superior LC with SBRT versus TACE (~2–4 times) [6–8]; also noted with HF-PBT [32]
	• **Consider SBRT over TACE where high risk of TACE-related toxicity, poor response to or progression after prior TACE, HCC with MVI where LRT is considered**
	Superior LC with SBRT versus RFA [11–14]; also noted with HF-PBT [17]
	• **Consider SBRT over RFA for larger tumors (especially subphrenic) and poor response to or progression after prior TACE**
	Limited data comparing SBRT and TARE with Y-90 suggests comparable LC [18,19]
OS and PFS	Similar OS following SBRT as compared to TACE [6–8], RFA [11,13], and TARE [18], where LRT has established role
	Extrapolate superior PFS with SBRT versus TACE from HF-PBT literature [32]
	Improved median OS (Δ 3.5 months) and PFS (Δ 3.7 months) with addition of SBRT to Sorafenib for locally advanced HCC with MVI [27]
	• **Await efficacy and safety data from future trials of current SoC systemic therapy (i.e. Atezolizumab/Pembrolizumab) +/- SBRT**
	• **Avoid off-trial concurrent SBRT and Atezolizumab/Bevacizumab, particularly when tumor proximal to luminal GI structures**
	• **Consider off-trial SBRT prior to Atezolizumab/Bevacizumab only upon MDD and individualized decision making**
Toxicity and QoL	Lower toxicity with SBRT versus TACE [6–8,33,34]
	Similar toxicity with SBRT as RFA and Y-90 [11–13,19]
	Similar toxicity and improved QoL when adding SBRT to Sorafenib [27]
	• **Use SBRT if LRT is considered for patients on TKI given no increase in toxicity**
Cost-effectiveness	Use of SBRT over TACE eliminates need for hospitalization [36]
	SBRT may have less treatment-related costs for patients and health systems than TACE and TARE [19,32,37]
Technical Considerations	SBRT allows optimized prescription of ablative dose to the entire tumor target across a range of tumor sizes and peritumor vascularity
	TACE may induce damage to peritumoral vasculature, creating hypoxic conditions promoting recurrence [9]
	RFA may be limited by the heat-sink effect, which may result in incomplete ablation of perivascular disease [15]
	TARE with Y-90 has unclear dosimetry; aggressive escalation of median (partial) doses less likely to predict treatment response than coverage of GTV with ablative dose [21,22]

Abbreviations: LC = local control; OS = overall survival; PFS = progression-free survival; QoL = quality-of-life; SBRT = stereotactic body radiotherapy; TACE = transarterial chemoembolization; HF-PBT = hypofractionated proton beam therapy; HCC = hepatocellular carcinoma; MVI = macrovascular invasion; LRT = locoregional therapy; RFA = radiofrequency ablation; TARE = transarterial radioembolization; Y-90 = Yttrium-90; PFS = progression-free survival; SoC = standard-of-care; GI = gastrointestinal; MDD = multidisciplinary discussion; TKI = tyrosine kinase inhibitor; GTV = gross tumor volume.

a LC rate of 100 % at 1 and 2 years, which was more than double the LC rate of TACE ($p = 0.019$). The worse LC of TACE may be attributable to treatment-induced damage to peritumoral vasculature, thereby creating hypoxic conditions that promote recurrence among sublethally-treated clones [9]. As we await the results of a multi-national phase 3 RCT of SBRT versus TACE for unresectable HCC (IAEA E33036) [10], we can advocate for SBRT over TACE in many scenarios including high risk of TACE-related toxicity, poor response to or progression post-TACE, and HCC with MVI if locoregional therapy is under consideration.

Superior LC is observed following SBRT versus RFA in large retrospective studies. Numerically higher freedom from local progression (FFLP) was reported for SBRT at 1 year (97.4 % vs 83.6 %) and 2 year (83.8 % vs 80.2 %) in a propensity score analysis of a single-center retrospective cohort with inoperable HCC (n = 224 patients [63 post-SBRT, 161 post-RFA], primarily CP-AB [11]. Re-ablations within 12 months, which occurred for 10 % of patients, were not considered local failures in this study. Accounting for early re-ablations, SBRT would have had an even greater advantage in FFLP. Subgroup analyses were performed to identify factors associated with improved LC in this study; although tumor size $\geq$ 2 cm was identified as favouring SBRT (HR 3.35 [95 % CI, 1.17–9.62], $p = 0.025$), BCLC stage was not included in the propensity matching. SBRT resulted in significantly higher local control (HR 0.45 [95 % CI, 0.35–0.58], $p < 0.001$), particularly for large (>3 cm) subphrenic tumors and after TACE, in a large multi-national propensity score analysis (n = 2064 patients, 1568 post-RFA and 496 post-SBRT, 88 % CP-A) accounting for BCLC factors [12]. Superior LC was durable in this analysis, with 3-year cumulative local recurrence rates of 21.2 % and 27.9 % following SBRT and RFA, respectively ($p < 0.001$). Study-level meta-analyses of published retrospective data have confirmed the superior LC of SBRT versus RFA, across three large propensity score studies matching BCLC factors (HR 0.39 [95 % CI, 0.30–0.51], $p < 0.001$) and 14 comparative studies (OR 0.45 [95 % CI, 0.36–0.56], $p < 0.001$) [13,14]. Prospective randomized data comparing the local effectiveness of SBRT and RFA across clinical scenarios is pending. Higher LC with SBRT may be extrapolated from a positive single-center phase 3 non-inferiority RCT of hypofractionated proton therapy versus RFA (144 patients, CP-AB7, $\leq$ 2 tumors, < 3 cm) [17], which demonstrated numerically higher local progression-free survival (LPFS) with PBT (94.8 %) than with RFA (83.9 %). A phase 3 non-inferiority RCT comparing FFLP following SBRT and RFA for small ($\leq$3 cm) unresectable HCC is underway (NCT05433701). The LC of RFA may be limited by the heat-sink effect, wherein convection cooling from large vessels may result in incomplete ablation of perivascular disease [15], as well as by tumor size and distance of tumor edge from the ablation zone [16]. In contrast, SBRT allows for prescription of ablative dose to the entire tumor. We can advocate for SBRT over RFA in situations including larger tumors, *peri*-vascular disease, and post-TACE, and appraise randomized data as it emerges.

Comparative LC outcomes for SBRT and TARE with Yttrium-90 (Y-90) are limited. Two single-center retrospective studies have been performed and published in abstract form [18,19]. Median FFLP was similar between SBRT and TARE (9 versus 8 months, $p > 0.05$) in a series of 239 patients (98 post-SBRT and 187 post-TARE with Y-90) with lesions < 10 cm or 1000 cc [18]. Similar 1-year LC was reported following SBRT and Y-90 (87 % vs 89 %, $p = 0.76$) in a cohort of 87 patients (24 post-SBRT, 63 post-TARE) [19]. Two prospective randomized studies (NCT05157451 and NCT04235660) were attempted but ultimately terminated due to lack of feasibility and inability to recruit patients. In the absence of strong comparative clinical data, some practitioners favour Y-90 over SBRT owing to the differential dosimetry of these modalities. Y-90 allows for greater extremes of intratumoral hot and non-ablative cold spots, due to radioembolization of neovasculature

Table 2
Summary of comparative outcomes of locoregional treatments from recent studies.

SBRT vs TACE	Study	Study Period	Study Design	Sample Size (n)	Baseline Characteristics and Inclusion Criteria	Median Follow-up (range)	Local Control	Overall Survival	Progression-free Survival	Toxicity	Quality-of-life	Cost-Effectiveness
	Sapir 2018 (6)	2006-2014	Retrospective, single-institution cohort	209	1-2 tumors, CP-AB	12.4 (NR) vs 23.0 (NR) months	1-year: 97% vs 47%, p < 0.001 2-year: 91% vs 23%, p < 0.001	1-year: 75% vs 74%, p = n.s. 2-year: 55% vs 35%, p = n.s.	NR	8% vs 13% CTCAE grade 3+, p = 0.05	NR	NR
	Comito 2022 (7)	2014-2019	Phase 3, randomized, single-center trial	40	1 prior course of TACE/TAE, 1-3 tumors (~58% 1 tumor), median tumor size 2.5 cm, BCLC-AB (84% B), CP-AB (77% A), KPS > 70%	20 months (3-56)	1-year: 84% vs 23%, HR 0.15 (95% CI, 0.04-0.4), p= 0.0002	Median: 31vs 30 months, p = 0.47	9 vs 4 months, HR 0.43, (95% CI, 0.21-0.87), p = 0.02	9% vs 3% CTCAE grade 1-2 0% vs 3% CTCAE grade 3 0% CTCAE grade 4+	NR	NR
	Romero 2023 (8)	2015-2020	Phase 2, randomized, multi-institution trial	28	Ineligible for further surgery or RFA, 1-3 tumors (100% 1 tumor), maximum cumulative diameter ≤ 6 cm, CP-A, ECOG 0-1,	28.1 months (12.5-51.3)	Time to local recurrence: >40 vs 12 months, HR 0.15 (95% CI, 0.02-1.21), p = 0.075 *100% at 1- and 2-years with SBRT, p = 0.019	Median: 44.1 vs 36.8 months, HR 0.58 (95% CI, 0.18-1.85), p = 0.36	NR	0% vs 13% treatment-related CTCAE grade 3+	Global health status (QLQ-C30), fatigue (QLQ-HCC18), and your health today (EQ-5D) scores stable for both modalities	NR
	Nugent 2017, 2018, 2020 (33, 34, 36, 37)	2014-2019	Phase 2, randomized, single-institution trial	54	Transplant-candidate, single tumor 2-5 cm or 2+ tumors <3 cm, CP-AB8, Zubrod PS ≤ 2	NR	Time to local recurrence: 10.4 (95% CI, 4.2-12.0) vs 9.2 (95% CI, 5.3-11.0) months	NR	NR	23% vs 65% Grade 2+	Δ PIQ-6 pain score: 0.7+/-4.5 vs 3.9+/-7.4 Δ PCS: -3.7+/-5.2 vs -2.0+/-4.8 Δ MCS: 3.3+/-5.7 vs -1.5+/-4.9	Total charges per patient: 62,531 vs 127,230 USD **Annual benefits of SBRT: 242,500 USD cost savings for hospital
SBRT vs RFA	Wahl 2016 (11)	2004-2012	Retrospective, single-institution cohort	224	1-6 tumors, tumor diameter <10 cm, CP-AC (90.2% AB)	13 (0.5-86.5) vs 20.0 (0.0-112.8) months	HR 3.84 (95% CI, 1.62-9.09), p = 0.002 1-year FFLP: 97.4% vs 83.6% 2-year FFLP: 83.8% vs 80.2% FFLP (tumors ≥ 2 cm): HR 3.35 (95% CI, 1.17-9.62), p = 0.025	1-year: 74.1% vs 69.6%, p = n.s. 2-year: 46.3% vs 52.9%, p = n.s.	NR	5% vs 11% CTCAE acute grade 3-4, p = 0.31 CTCAE late grade 3-4 biliary: 2-year: 3.3% vs 6%, p = 0.38 CTCAE late grade 3-4 luminal GI: 2-year: 8.3% vs 6.4%, p = 0.66 CP decline: OR 1.02 for RFA, p = 0.97	NR	NR
	Kim 2020 (12)	2010-2016	Retrospective, multi-institution cohort	2064	1+ tumors (~90% 1 tumor), median tumor size 2.0 cm (20.6% > 3 cm), CP-AC (88.3% A), BCLC-0C, ECOG 0-3 (96.4% ECOG 0-1).	27.7 months (13.8-45.6)	HR 0.45 [95% CI, 0.35-0.58], p < 0.001 3-year CLRR: 21.2% vs 27.9%, p < 0.001 2-year CLRR for > 3 cm subphrenic tumors: 18.7% vs 32.1%, p = 0.019 Superior LC with SBRT after TACE (p = 0.001)	2-year CMR: 22.4% vs 28.9%, p = 0.31	NR	1.6% vs 2.6% CTCAE acute grade 3-4, p = 0.27 11.2% vs 4.7% Δ CP of >2 at 3 months, p < 0.001 6.3% vs 8.1% Δ CP of >2 at 6 months, p = 0.28	NR	NR
	Eriguchi 2021 (13)	NA	Study-level meta-analysis	931- OS 838- LC	Propensity-matched studies including BCLC stage	NR	HR 0.39 (95% CI, 0.30-0.51), p < 0.001	HR 0.89 (95% CI, 0.74-1.08), p = 0.24	NR	NR	NR	NR
	Rim 2022 (14)	NA	Study-level meta-analysis	2875 - OS 2974 - LC	Comparative studies	NR	OR 0.45 (95% CI, 0.36-0.56), p < 0.001	OR 1.25 (95% CI, 0.92-1.71), p = 0.15	NR	NR (not specific to HCC)	NR	NR
SBRT vs TARE	Liang 2021 (18)	2017-2020	Retrospective, single-institution cohort	239	Tumor size <10 cm, treatment volumes <1000 cc, 62% vs 80% CP-A	11 months (0-44)	Modality not independent predictor of LC (p = n.s.)	Median: 24 vs 21 months, p = n.s.	NR	NR	NR	NR
	deBettencourt 2021 (19)	2018-2020	Retrospective, single-institution cohort	87	NR	315 days (NR)	1-year: 87% vs 89%, p = 0.76	NR	NR	50.0% vs 52.4% treatment-related, p = 0.99	NR	Total charges per patient: 12,885 vs 19,393 USD
SBRT + ST vs ST	Dawson 2023 (27)	2013-2021	Phase 3, randomized, multi-institution trial	177	Unsuitable for resection, transplant, RFA, TACE, CP-A, BCLC-BC (82% C), Zubrod PS ≤ 2, 74% MVI (63% advanced), 4% metastases, ≤ 5 tumors, maximum sum of diameters 20 cm	13.2 months for all (NR), 33.7 months for alive (NR)	NR	Median: 15.8 (95% CI, 11.4-19.2) vs 12.3 (95% CI, 10.6-14.3) months *** HR 0.72 (95% CI, 0.52-0.99), p = 0.042	9.2 (95% CI, 7.5-11.9) vs 5.5 (95% CI, 3.4-6.3) months HR 0.55 (95% CI, 0.40-0.75, p = 0.0001	47% vs 42% CTCAE grade 3+, p = 0.52	35% vs 10% increase in FACT-Hep score	NR

Abbreviations: SBRT = stereotactic body radiotherapy; TACE = transarterial chemoembolization; CP = Child-Pugh; NR = not reported; CTCAE = Common Terminology Criteria for Adverse Events; TAE = transarterial embolization; BCLC = Barcelona Clinic Liver Cancer; KPS = Karnofsky Performance Status; RFA = radiofrequency ablation; ECOG = Eastern Cooperative Oncology Group; QLQ-C30 = EORTC Core Quality-of-Life Questionnaire; QLQ-HCC18 = EORTC Quality-of-Life Questionnaire – Hepatocellular Carcinoma/Primary Liver Cancer Module; EQ-5D = European Quality-of-Life 5 Dimensions Questionnaire; PS = performance status; PIQ-6 = Pain Item Questionnaire (6 itmes); PCS = physical component summary of Short Form 36 (SF-36) Health Survey; MCS = mental component summary of Short Form 36 (SF-36) Health Survey; USD = United States Dollars; FFLP = freedom from local progression; GI = gastrointestinal; CLRR = cumulative local recurrence rate; LC = local control; CMR = cumulative mortality rate; OS = overall survival; HCC = hepatocellular carcinoma; TARE = transarterial radioembolization; ST = systemic therapy; MVI = macrovascular invasion; FACT-Hep = Functional Assessment of Cancer Therapy - Hepatobiliary.
* Post-hoc, per-protocol analysis.
** Assuming 60 patient per year.
*** After adjustment for PS, metastases, CP-A5 vs 6, degree of MVI.

heterogeneously distributed within tumors, while SBRT generates a comparatively homogenous distribution of ablative dose throughout tumors [20]. Enthusiasm for Y-90 has increased with the publication of the LEGACY trial, a multi-center retrospective single arm study in which very high median doses (410.1 Gy, range: 199.7–797.6 Gy) were delivered to solitary unresectable HCC and complete pathologic necrosis was noted with doses in excess of 400 Gy [21]. Although these median doses are higher than what can be delivered with SBRT, they may not be necessary for durable local control. Confounding by indication may impact the attribution of high median doses to response, as tumors amenable to high doses may also be more amenable to volumetric coverage by ablative dose. Coverage of the gross tumor volume with ablative dose, rather than aggressive escalation of median (partial) doses, is likely to better predict treatment response to Y-90 for HCC [22]. When volumetric dose coverage is ablative, even modestly high prescription doses yield excellent LC outcomes following SBRT [23,24]. We must better understand the dosimetry of high-dose Y-90 radioembolization and quantify the comparative effectiveness of SBRT and Y-90 radioembolization as locoregional therapies.

Overall and progression-free survival

While SBRT results in a similar overall survival (OS) as TACE, RFA, and TARE across comparative effectiveness studies in unresectable HCC without MVI [6–8,11,13,18], the addition of SBRT to systemic therapy may improve OS and progression-free survival (PFS) for locally advanced HCC with MVI. This is a clinical scenario where other locoregional therapies have yet to demonstrate an additive survival advantage and the current standard-of-care is systemic therapy alone [2–4,6,25,26]. SBRT prior to Sorafenib improved median OS (15.8 vs

12.3 months, p = 0.0554) and PFS (9.2 vs 5.5 months, p = 0.0001) in RTOG 1112, a multi-center phase 3 RCT in 177 patients (CP-A, Zubrod performance status 0–2) with HCC unsuitable for resection, transplant, RFA, or TACE [27]. Patients on this trial had very advanced disease: 82 % were BCLC- C, 74 % had MVI (63 % with advanced degree of MVI), metastases (4 %), and five or less tumors with median sum of maximum diameter 6.7 cm in the SBRT arm (maximum 20 cm allowed). The OS benefit in RTOG 1112 was statistically significant (HR 0.72 [95 % CI, 0.52–0.99], p = 0.042) after adjusting for performance status, metastases, CP-A5 versus 6, and degree of MVI. Since the inception of RTOG 1112, the standard-of-care systemic therapy for patients with locally advanced HCC has changed from Sorafenib to the combination of Atezolizumab and Bevacizumab [2–4]; as such, the trial was closed early. Clinical trials will be required to assess the OS and PFS benefit of adding SBRT to Atezolizumab and Bevacizumab in unresectable HCC with MVI, as well as the ideal sequence of local and systemic therapy. To date, the combination of SBRT and immunotherapy appears to be safe in the treatment of HCC [28,29]. Limited retrospective evidence suggests that high-dose radiotherapy combined with Atezolizumab and Bevacizumab may be well-tolerated [30]. A phase 1 trial is underway assessing the safety of SBRT delivered during cycles of both Atezolizumab and Bevacizumab in the treatment of HCC (NCT05488522). Until safety data from clinical trials are reported, concurrent use of SBRT and these agents, particularly Bevacizumab, is not recommended. Concurrent use of Bevacizumab and SBRT is not recommended for tumors proximal to luminal gastrointestinal (GI) structures, due to the potential risks for perforation and bleeding [31]. SBRT prior to Atezolizumab and Bevacizumab for unresectable HCC with MVI should only be considered upon multidisciplinary discussion and individualized decision making, considering limited locoregional options for aggressive tumors, potential delays in starting systemic therapy (e.g. if awaiting variceal banding), and the pattern of failure among these patients. The role of SBRT in first-line treatment for unresectable HCC with MVI will continue to be refined in future clinical trials in the coming years.

Extrapolating from the proton therapy literature, SBRT may also improve PFS compared to TACE for unresectable HCC amenable to locoregional therapy. Hypofractionated proton therapy was associated with a significant improvement in median PFS compared to TACE (not reached versus 12 months, p = 0.002) in a multi-center phase 3 trial of 74 patients (CP-AB) with unresectable HCC not previously treated with locoregional therapy [32]. Although there are differences between photon and proton radiotherapy, it may be reasonable to infer a PFS benefit with any high-dose conformal radiotherapy for this population. NRG GI003 (NCT03186898), an on-going multi-center phase 3 RCT comparing proton and photon radiotherapy, will help determine whether oncologic outcomes are superior with proton therapy.

Toxicity and quality of life

SBRT has lower toxicity than TACE and similar toxicity to RFA and TARE. Grade 3 + toxicity was lower following SBRT versus TACE in retrospective and prospective studies (0–8 % vs 13) [6,8]. Grade 2 + toxicity was lower following SBRT (23 % versus 65 %) in the preliminary analysis of a single-center phase 2 feasibility RCT of bridging SBRT versus TACE (NCT02182687) [33]. Higher quality-of-life (QOL) scores were also reported in terms of post-treatment improvement in pain in this trial [34]. The complete study manuscript is pending for this trial and a multi-center phase 3 trial (NCT03960008) is underway from the same group, further comparing these two bridging therapies [35]. SBRT and RFA have equally low toxicity rates (0–11 %) with no statistical differences (p > 0.05) across propensity score analyses of single-institutional and multi-national experiences [11–13]. Similar (p = 0.99) treatment-related toxicity rates were also reported between SBRT (50 %) and TARE with Y-90 (52.4 %) in the single-institutional retrospective experience reported by deBettencourt et al [19]. While RTOG 1112 reported no difference in treatment-related grade 3 + toxicity rates between SBRT added to Sorafenib (47 %) and Sorafenib alone (42 %) for patients with locally advanced disease (p = 0.52) [27], it also reported greater improvement in QoL at 6 months post-treatment with SBRT and Sorafenib (35 %) than with Sorafenib alone (10 %). The low toxicity rates and favourable quality-of-life (QoL) outcomes of SBRT make it an attractive locoregional therapy across clinical indications for unresectable HCC, especially when Sorafenib or other tyrosine kinase inhibitors are being considered.

Cost-Effectiveness

We must limit the financial toxicity of locoregional therapy for patients and health systems. SBRT may be more cost-effective than TACE and TARE. Using SBRT instead of TACE eliminates the need for post-treatment hospitalization [36], as patients receiving TACE are often hospitalized after each of treatment while those receiving SBRT are not. This is estimated to result in 242,500 United States Dollars (USD) of annual cost savings for hospitals, due to reduced inpatient days [37]. Furthermore, SBRT is associated with less treatment-related costs than TACE. The total cost of 5-fraction SBRT was calculated as 45,083 USD and cost of fiducials calculated as 17,448 USD, for a total cost of 62,531 USD [37]. In comparison, total cost of TACE with two treatments was 127,230 USD. Underscoring the cost-effectiveness of radiotherapy over TACE, significantly fewer days of post-treatment hospitalization were noted with hypofractionated proton therapy than with TACE (24 vs 166, p < 0.001) and total mean cost per patient was 28 % lower for those who received proton therapy (25,410 USD) rather than TACE (35,484 USD) [32]. Limited data comparing SBRT and TARE also suggest improved cost-effectiveness with radiotherapy (12,885 versus 19,393 USD) [19].

Seventh-inning Stretch

We should continue to improve upon the strengths of SBRT as a locoregional therapy for HCC and expand indications for its use as a standard-of-care treatment option. A number of emerging strategies may further widen the therapeutic index of SBRT in HCC.

SMART: Stereotactic magnetic resonance-guided adaptive radiotherapy

Uncertainties in SBRT planning and delivery limit the ablative dose safely delivered to tumors abutting hepatobiliary and luminal GI organs-at-risk (OAR). SMART reduces these uncertainties by using on-table MR imaging from an MR-linear accelerator for daily anatomical and positional adaptation and motion management [38], thereby permitting reductions in planning target volumes (PTV) and dose escalation. Prospective single-arm and retrospective studies of SMART for HCC, cholangiocarcinoma, and liver metastases have shown 2-year LC of 73–100 % (median: 80 %), grade 3 toxicity of 0–8 %, and no grade 4 + toxicity following biologically effective dose (BED_{10}) prescriptions of 72–105 Gy (median: 93 Gy) [39]. Contrasting with HCC, liver metastases may have higher LC with BED_{10} > 100 Gy [23,24,40]; RASTAF (NCT04242342), an ongoing phase 2 non-randomized trial of SMART for liver tumors, is investigating dose-escalation with 50 Gy in 5 fractions (BED_{10} = 100 Gy) for tumors near OARs and 60 Gy in 5 fractions (BED10 = 132 Gy) for tumors away from OARs. To assess non-inferiority in Grade 3 + GI and hepatobiliary toxicity between SMART and conventional cone-beam CT guided-SBRT, the phase 2 MAESTRO study (NCT05027711) randomizes liver metastases amenable to $BED_{10} \geq 100$ Gy to one of these treatments.

Intensity-modulated stereotactic body proton therapy

Protons can be used to reduce the integral liver dose associated with photon SBRT, potentially minimizing the risk of hepatic toxicity associated with radiotherapy [41]. A retrospective single-institutional review of stereotactic body proton therapy (SBPT) for 81 liver metastases in 46 patients, 56.5 % of whom had two or more treated tumors,

reported no grade 3 + toxicities [42]. Conformality and toxicity of SBPT with passive-scatter technology may be further improved by utilizing modern radiotherapy techniques for planning (e.g. robust optimization) and delivery (e.g. pencil beam scanning, fiducial-based or cone-beam CT image-guidance) allowing intensity modulated proton therapy (IMPT). A low median value mean liver dose (12.3 Gy relative biological effectiveness) and percentage of patients having a 2 + increase in CP score (16 %) was reported in the single published series of IMPT, including SBPT (7/37 patients), for HCC [43]. There are challenges associated with dose delivery with intensity-modulated SBPT due to particle range uncertainties, target motion, and interplay effect, necessitating further investigation of clinical outcomes in larger series. A phase 2 single-arm trial of SBPT for HCC (NCT04805788) is in-progress; the primary endpoint is the 3-month rate of patients having a 2 + increase in CP score, and secondary endpoints include other toxicity and oncologic outcomes.

Single-fraction SBRT

Single-fraction SBRT is an appealing radiotherapy strategy for selected lesions away from the biliary tree and luminal GI structures, potentially offering comparable convenience with other locoregional therapies, less interference with systemic therapy, and higher cost effectiveness. There is growing data for single-fraction SBRT of liver metastases demonstrating low toxicity and excellent control with doses of 18–40 Gy [44,45]. Long-term outcomes of single-fraction SBRT from larger series are warranted to ensure efficacy and safety.

Novel SBRT and systemic therapy combinations

Innovative strategies are required to exploit the immune-modulating properties of SBRT in various permutations and combinations with immunotherapy, thereby potentiating further improvements in both local and systemic control in HCC. The addition of immunotherapy to SBRT has demonstrated gains in 12-month OS (92 % vs 74 %, $p = 0.034$) and objective response rate (88 % vs 50 %, $p = 0.006$) in a propensity score analysis of a retrospective multi-institution cohort with ≤ 3 unresectable HCC tumors (n = 75 patients [25 post-SBRT and immunotherapy, 50 post-SBRT alone], Child-Pugh [CP]-A5-B7) [29]. Preclinical studies are needed to better understand the synergies of SBRT and immunotherapy, particularly regarding optimal immunogenic treatment volumes and dosing, predictive biomarkers of treatment response, and the role of HCC tumor microenvironment in modulating this response [46]. While RTOG 1112 tested a sequential strategy of SBRT followed by systemic therapy, the sequencing and timing of these treatment modalities merit further investigation to maximize efficacy and safety. Personalized ultrafractionated stereotactic adaptive radiation therapy (PULSAR) is a paradigm wherein fractions of high dose radiation are given weeks apart to allow for interfractional biologic change to ensue. When combined with immunotherapy, PULSAR is hypothesized to synergistically maximize anatomic adaptation and systemic response in HCC [47]. Clinical studies of this approach are awaited to support the feasibility and efficacy of this approach [48].

Neoadjuvant SBRT

SBRT could be considered in neoadjuvant treatment strategies for patients with locally advanced HCC [33–36], extrapolating from its use as a bridge to transplant. An RCT of neoadjuvant radiotherapy for resectable HCC with tumor thrombus of the portal vein main trunk or side branches (n = 164 patients [82 neoadjuvant radiotherapy, 82 hepatectomy alone]) demonstrated significant improvements in 12-month post-operative OS, HCC-related mortality (HR 0.35 [95 % CI, 0.23–0.54], $p < 0.001$), and HCC recurrence rates (HR 0.45 [95 % CI, 0.31–0.64], $p < 0.001$) [49]. Multi-modality neoadjuvant combinations of SBRT with local and systemic therapies may also hold promise. START-FIT, a prospective single-arm phase 2 trial (n = 33 patients, CP A5-B7), showed that a neoadjuvant regimen consisting of TACE (day 1), followed by SBRT (day 28) and then Avelumab (14 days post-SBRT) converted 55 % of patients with locally advanced, initially unresectable HCC towards curative treatment [50]. Further work in this space may expand the indications for SBRT and increase the number of patients who can benefit from curative management.

Winning Today's Games

We need as many home runs as possible to address unmet needs of patients with HCC, amidst rising global incidence and limited established locoregional treatment options for patients with advanced disease [4]. SBRT adds to the oncologic armamentarium with attractive advantages in LC, survival, morbidity, and cost-effectiveness. Promising data from single-center or small phase 2 RCTs have added to the evidence base for radiotherapy in unresectable HCC [8,32], thus far deemed low-to-moderate quality in clinical practice guidelines [3]. In the spirit of Carl Sagan, the absence of high-quality evidence is not high-quality evidence of absence. Additional multi-institutional phase 3 RCTs are awaited to substantiate use of SBRT with the highest quality comparative evidence. We must advocate for multidisciplinary support of such trials, as we need speedy accrual to obtain the level of evidence we all desire to inform contemporary practice [7,27].

As we await further comparative evidence for SBRT and associated emerging strategies in HCC, we can continue advocating for consideration of this treatment modality in the daily multidisciplinary management of patients with HCC. We can advocate for SBRT locally by discussing cases at tumor board conferences, educating multidisciplinary colleagues about the comparative advantages of SBRT as a locoregional therapy (Tables 1 and 2), and encouraging referrals of all patients considered for locoregional therapy to both Interventional Radiology and Radiation Oncology (RO). We can advocate for SBRT internationally by increasing our participation as ROs in disease society committees, lobbying for inclusion of SBRT in multidisciplinary management guidelines [5], and updating SBRT guidelines to provide guidance and caution for complex contemporary clinical situations, such as peri-Bevacizumab SBRT, re-irradiation, SBRT after prior Y-90 TARE, and significant multifocal disease. The future is bright for SBRT In the management of unresectable HCC, and with continued efforts, we hope more patients can benefit from this excellent standard-of-care treatment.

CRediT authorship contribution statement

Amir H. Safavi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Laura A. Dawson:** Data curation, Formal analysis, Supervision, Writing – review & editing. **Aruz Mesci:** Conceptualization, Data curation, Formal analysis, Supervision, Writing – review & editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: LAD has received royalties from Raysearch Laboratories (paid to institution). AHS and AM declare no conflicts of interest.

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