REVIEW

Current Understanding of Ablative Radiation Therapy in Hepatocellular Carcinoma

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Abstract: The role of ablative stereotactic body radiotherapy (SBRT) in hepatocellular carcinoma (HCC) has been evolving over the last few decades. SBRT has mostly been used in early stages of HCC, including few (≤ 3 in number) tumors, small tumours (< 3 cm in size), as well as larger tumours which are ineligible for other ablative modalities, mostly without vascular invasion. In early stage HCC, SBRT is used as a definitive treatment with curative intent or with intent to bridge to liver transplant. Retrospective and prospective institutional series document a high rate of local control (68–95% at 3 years) following SBRT. This coupled with a low risk of toxicity makes this non-invasive ablative treatment an attractive option for patients who are ineligible for other ablative treatments. Small randomized studies of ablative radiation have also shown non-inferiority of radiation as compared to radiofrequency ablation (RFA). Currently, SBRT is widely available as a safe and effective liver directed therapy, although there is a need for more studies providing higher level evidence. This review gives a brief overview of SBRT and the evidence for its use in HCC patients with ablative intent.

Keywords: hepatocellular carcinoma, radiotherapy, stereotactic body radiotherapy, SBRT, stereotactic ablative radiotherapy, SABR

Introduction

Stereotactic body radiotherapy (SBRT) was first used to treat patients with hepatocellular carcinoma (HCC) almost 20 years ago, but still there is a limited amount of high level evidence for its efficacy.[1,2] Hepatocellular carcinoma (HCC) is the 7th most common cancer in the world in terms of incidence and the 3rd highest in terms of mortality.[3] Even though only 15–20% of HCC patients are eligible for other ablative liver directed treatments (resection, liver transplant, radiofrequency ablation), radiation therapy (SBRT, protons or conformal radiotherapy) is often not included as a treatment option in the BCLC classification due to the lack of high-power randomized trials. The Modified Barcelona Clinic Liver Cancer (BCLC) classification system classifies HCC into Stage 0, A, B, C and D on the basis of various prognostic factors including tumor size, tumor number, liver function and the patient's performance status.[4] The definition of BCLC A, or "early stage HCC", as per the Modified BCLC staging system includes up to 3 tumor nodules ≤ 3 cm in size in patients with preserved liver function (Child Pugh A without ascites) and excellent performance status (PS 0), but other definitions of early stage HCC are also used clinically. For example, the AJCC/UICC TNM classification system includes tumors up to 5 cm in size as Stage I

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& II disease.[5] This variability in the definitions of "early stage" HCC is reflected in the heterogeneity of patients included in the various studies reporting outcomes of SBRT. It is generally agreed that small (< 3 cm in maximum dimension) and limited tumor number (<5 in number) confined to the liver with no vascular invasion or extrahepatic spread mostly fall into the category of early HCC. The BCLC classification that gives a broad purview of first line treatment options on the basis of currently available evidence, has been the backbone of HCC treatment guidelines from organizations like the European Association for the Study of Liver Diseases (EASLD) and the American Association for the Study of Liver Diseases (AASLD), and for the purpose of this review, the BCLC definition of early stage HCC will be used, although there is also increasing evidence for SBRT for more advanced stage disease. At the same time, we acknowledge the limitations of the currently available data and emphasize the need to include more homogenous patient populations in future studies, so that the evidence base for SBRT in this patient population is not subject to the lack of power inherent in heterogenous cohorts. Uniform use of a single criterion/definition across the scientific community in future planned studies, will help to easily compare results from different institutions.

Radiation therapy was first used in the treatment of primary liver cancer in the 1980s, although generally as a palliative treatment targeting the whole liver. Early reports quickly recognized the possibility of radiation induced liver disease. The advent of 3-dimensional conformal techniques greatly improved the ability to deliver tumoricidal doses to a part of the liver while sparing the remaining normal functional liver. Three-dimensional conformal radiotherapy (3-DCRT) was developed in the 1990s when newer technology became available in the form of computerized treatment planning systems, used to calculate radiation doses in a 3-dimensional model of the patient body acquired using a CT scan, and deliver ionizing radiation therapy using multi-leaf collimators and computer-controlled treatment machines. 3-DCRT enabled the delivery of more conformal dose distributions than hitherto possible, thus increasing the therapeutic ratio. 3-DCRT, when used in the treatment of early HCC, has been reported to provide local control rates of 71.4% to 93.8% and overall survival of 73.6% to 81.1% at 1 year.[6,7] With the advent of intensity modulated radiotherapy (IMRT), the use of multiple fields and the modulation of the radiation dose intensity within the individual fields

enables more conformal irradiation of irregularly shaped targets. The use of stereotactic principles and modern 3-DCRT, IMRT or volumetric arc therapy (VMAT) have further enabled the delivery of very high doses within the target volume with a sharp dose gradient outside the target volume, limiting dose to surrounding liver and normal tissues further. Daily image-guidance and respiratory motion management also characterize modern liver stereotactic body radiation therapy (SBRT) and are associated with the delivery of hypofractionated doses of radiation in a limited number of treatment sessions/fractions. The study of the tolerance of the normal liver and development of stereotactic techniques led to the adoption of SBRT as a technique of effectively treating liver tumors, although early reports generally included at least a subset of patients with advanced HCC.[8,9] Subsequently, several institutions presented series of early HCC treated with high dose ablative radiation therapy, many including HCC > 5 cm,[10] mostly these being patients ineligible for other ablative liver-directed therapies such as surgical resection, radiofrequency ablation (RFA) or microwave ablation (MWA).

The dosimetric advantage of using charged particle therapy to treat liver tumors was also explored by several institutions in Japan, Korea and the United States of America. Use of charged particles like protons or carbon ions instead of photons results in greatly reduced radiation dose deposited distal to the beam, enabling more conformal dose distributions and sparing more normal liver. The University of Loma Linda,[11] the Massachusetts General Hospital[12] and the University of Tsukuba[13] have all published their experiences with proton therapy as has a multi-institutional Phase II study in the USA which reported 2-year local control of 94.8% in unresectable HCC.[14] The Synchrony™ Respiratory Tracking System of the Cyberknife® Robotic Radiosurgery system is another platform for SBRT utilizing a linear accelerator mounted on a robotic arm to deliver multiple non-coplanar beam arrangements to the target while also tracking the tumor in real-time. Disadvantages of Cyberknife include the need for fiducial markers, especially to localize small early HCC. Magnetic resonance imaging (MRI) is also being explored to improve the accuracy of all steps in the process of delivering SBRT – from target delineation to treatment delivery as well as assessing response to SBRT. The use of MRI to guide target delineation is well established due to the greater clarity in depicting the extent of intrahepatic disease, as well as the information it

provides regarding extent of motion of the liver/tumor.[15] It is also used routinely in the clinic in assessing response post SBRT.[16] The use of MRI in on-board image guidance during radiation delivery is being explored and expanded with the clinical availability of MR-Linear accelerators.[17,18]

This review proposes to summarize the existing literature for the role of SBRT in HCC, focusing on the role of ablative radiotherapy in treatment of HCC, ie mostly tumors up to 3 cm in size. The radiobiological rationale behind the use of SBRT in early HCC is first described, followed by a review of existing evidence on the indications and outcomes of SBRT in this setting, highlighting studies that have compared SBRT to other treatments in early stage HCC patients. Further, controversies in the use of SBRT for early stage HCC are addressed as well as the future directions on this topic.

Rationale Behind Use of SBRT in Early HCC

SBRT refers to the use of hypofractionated doses of radiation in a limited number of sittings (typically less than or equal to 5) to ablate the tumor cells while causing minimal damage to surrounding normal liver through the use of highly conformal techniques.

The "5 R's of radiobiology", ie repair, reoxygenation, redistribution, repopulation and radiosensitivity are used to describe the mechanisms of cell response to conventionally fractionated external beam radiation, and the differential response of tumors versus normal tissues to radiation therapy is the basis for why radiation therapy has conventionally been delivered over many fractions. Techniques to focus radiation therapy with high precision and accuracy mean there is less need for prolonged fractionation. The effect of hypofractionated dose of radiation on tumor response, as typically used in SBRT, seemed to be supradditive to what could be explained by traditional radiobiological mechanisms. In SBRT, repair is hardly possible as the high dose delivered per fraction causes more necroptosis than apoptosis, therefore the majority of cells will suffer from lethal DNA damage rather than sublethal damage and die. Redistribution within the cell cycle is similarly rendered ineffective as the cell cycle is completely blocked at all stages after high dose irradiation – cells in both the sensitive and insensitive phases of the cell cycle are directly killed.[19] While tumor hypoxia may persist after vascular injury due to SBRT, and

reoxygenation may not be possible due to the relatively short duration of treatment, theoretically SBRT negates the effect of reoxygenation by causing direct cell kill of both normoxic and hypoxic tissues effectively due to the high doses delivered. SBRT also typically has shorter schedules than conventional fractionation, usually 1–2 weeks, thus giving cells no time to repopulate. Besides these mechanisms of direct cell kill, high dose SBRT has been shown in pre-clinical models to act through two additional mechanisms – vascular endothelial injury and immune cell activation. Endothelial apoptosis which is induced at single doses above ~8–11 Gy, has anti-angiogenic effect in the tumor vasculature.[20] Moreover, doses above 10 Gy induce vascular injury causing hypoxia, tumor microenvironment acidification and indirect death of tumor cells.[21] Through increased vascular permeability and apoptosis, as well as endothelial injury induced platelet aggregation and thrombosis, SBRT further exacerbated hypoxia induced tumor necrosis. SBRT also recruits immune cells through activation of inflammatory cytokines such as IL-1 and TNF, resulting in an intense infiltrate of the tumor and distant sites by a cytotoxic CD-8+ cell infiltrate. Direct cell ablation by SBRT also releases tumor antigens profusely which are presented very effectively by these activated immune cells and further lead to immune cell activation and tumor cell kill, resulting in a vicious cycle of cell kill by immune mechanisms.[22] Due to these direct cell-kill effects, SBRT can effectively ablate early HCC lesions and the parallel architecture of the functional subunits in the liver ensure that as long as a critical volume of normal liver is left unirradiated, the tumors can receive adequately ablative doses. In early HCC, the number of lesions is usually limited such that delivering ablative doses to these should be possible with negligible rates of toxicity, especially if the Child Pugh score is A or early B.

Evidence for Indications and Efficacy of SBRT in Early HCC

Traditionally, early stage HCC patients are treated with resection to provide cure in non-cirrhotic livers or in cirrhotic patients without portal hypertension, or with orthotopic liver transplant for selected early stage HCC patients, including those with impaired liver function.[4] The use of locally ablative techniques such as radiofrequency ablation (RFA) is standard of care in cirrhotic livers. RFA in well-selected tumors (< 3 cm in size and technically accessible) results in high local control rates similar to

surgical resection, ie more than 90% at 3–5 years. However, only a minority of patients with early HCC are eligible for transplant (due to a limited donor pool), surgical resection or RFA due to tumor factors (size, number), liver function (Child Pugh score, portal hypertension), technical factors (location of tumor, proximity to large vessels) and general medical factors (coagulopathies, poor performance status). Hence there is a proportion of patients who require non-invasive ablative liver-directed therapies. These are currently the primary candidates who undergo external beam radiation using SBRT. Patients who have recurred following other local regional therapies are also candidates for SBRT.

There are 2 main indications for SBRT in early hepatocellular cancer – as definitive treatment, or as bridging treatment to orthotopic liver transplant. The target volumes and dose fractionation may be different when applied to each of these indications and the goals of care and outcomes of these two groups are different, as survival is largely driven by the use of liver transplantation in the latter category.

Definitive Treatment of Early HCC

Several institutions have reported their retrospective and prospective experiences with SBRT for early HCC's. Although many of the series have included a proportion of patients with advanced tumors, some have reported outcomes separately for early and advanced HCC. The early series from Korea and Japan mostly focus on treatment of early stage HCC which were ineligible for or failed other ablative therapies[23–29] (Table 1). These series reported local control rates ranging from 67.5% to 97% at 3 years and overall survival rates of 39% to 84% at 3 years. Recent multi-institutional series from these countries though report outcomes of patients who were treated with SBRT upfront as first line of treatment, indicating a more widespread adoption/acceptance of SBRT in treatment of early tumors.[30–37]

Bridging to Transplant

Liver transplant is a curative treatment option for patients with HCC with background cirrhosis as it treats both the cancer as well as the cirrhosis. However, only patients with early stage HCC (eg within Milan criteria) are eligible for transplantation, and patients usually have to wait many months before an appropriate organ is available. In the interim, "bridging therapies" are used to prevent the tumor from progressing beyond transplant criteria. The most common bridging therapies include RFA/MWA and TACE, but SBRT has also been used effectively as a bridging therapy.[38–40] SBRT has also been associated with pathological responses in the explanted livers ranging from 27% pathological complete responses to 73% pathological partial responses.[41]

This has been well tolerated with minimal toxicity and minimal drop-off from the waiting list. However, ultimately, orthotopic liver transplant drives the extremely good outcomes seen in this group.

Comparison of SBRT with Other Techniques

There are no large randomized controlled trials comparing SBRT to either surgical resection, RFA or TACE in early HCC. Below are summarized the available evidence (including some small RCT's and a recent non-inferiority Phase 3 RCT) comparing outcomes of SBRT with those of other liver-directed therapies such as RFA, TACE and surgical resection commonly used in early stage HCC.

Radiofrequency Ablation (RFA)

Wahl et al have reported a propensity-score matched analysis of patients treated with RFA or SBRT at a single institution and found that SBRT resulted in better local control in tumors larger than 2 cm[42] (Table 2). Comparative analyses of outcomes and cost with SBRT and RFA for early HCC using the SEER database by Parikh et al concluded that there was no significant difference in survival, 90-day hospitalization, or costs of treatment with RFA vs SBRT.[43] Hara et al also conducted comparative propensity-score matched analyses between RFA and SBRT in small early HCC and reported similar excellent local control and survival in similarly selected patients.[44] In contrast, Rajyaguru et al in a retrospective analysis from the National Cancer Database in patients with Stage I and II HCC treated with RFA or SBRT showed that RFA results in better overall survival; however several limitations of the data used for this analysis have been pointed out, including the lack of the baseline characteristics which are commonly used to decide patient selection for one of these two treatment modalities.[45] More recently, a Markov model analysis compared the predicted OS of patients with small HCC (<3 cm, < 3 nodules, CP A or B with no vascular invasion) after RFA or SBRT. As per this modelling study, no significant difference in predicted overall survival was observed in both cohorts.

Table 1 Selected Series of Stereotactic Body Radiotherapy (SBRT) for Hepatocellular Carcinoma (HCC)

Author	Year	N	Tumour Size Median (Range)	Dose	LC	OS	Toxicity	Comments
Kwon et al[23]	2010	42	Median volume= 15.4 cc (3.0–81.8 cc)	30–39 Gy/3# to 75–80% isodose	3-yr LC=68%	3-yr OS=59%	One patient died with extrahepatic metastasis and radiation-induced hepatic failure	Cyberknife; no planned therapy, eg TACE, prior to SBRT
Choi et al[25]	2008; retrospective	22 (+9 with PVT)	Median volume= 23.5cc (3.6–57.3 cc)	30–39 Gy/3# to 75–80% of target volume	Overall Response rate= 83%	Median OS= 12m (of small HCC alone)	10% progression of CP;3% Grade 3 liver enzyme toxicity	Cyberknife; small HCC were treated with SBRT alone (lesions with PVT underwent SBRT +TACE)
Jang et al[26]	2013; retrospective	74 (+8 with PVT)	Median size=3 cm (1–7 cm)	Median 51 Gy in 3# (33–60Gy)	2-yr LC=87%	2-yr OS=63%	6%-> Grade 3 GI toxicity; 7%-deterioration of CP score by >2.	Unsuitable for surgery/local ablation/had incomplete response to TACE (all patients underwent TACE, although not planned); LINAC-based SBRT; Dose response threshold at 45–54 Gy EQD2
Yoon SM et al[29]	2013	93	Median size=2 cm (1–6 cm)	30–60Gy in 3–4 #	3-yr LC=92%	3-yr OS=54%	6.5% ≥Grade 3 hepatic	LINAC based SBRT-static conformal, no planned TACE
Sanuki et al[27]	2014; retrospective	185	Median size=2.4–2.7 cm (0.8–5 cm)	35Gy/5# 40Gy/5#	3-yr LC=91%	3-yr OS=70%	Acute toxicities ≥ Grade 3 observed in 13.0% patients; 10.3% patients had worsening of CP score by 2 points. 2 patients had grade 5 liver failure	2 cohorts- dose as per size; no planned TACE
Qiu et al[33]	2018; retrospective	93; 86% no PVT	Median sum of longest diameter= 4.4 cm (2.9–5.8)	50–60 Gy/ 5-10#	At median follow up of 4 months, 94% had CR,PR or SD	Median OS =9 m	Adverse events ≥ Grade 3 were 10%	46% Child-Pugh Class B or C; no planned therapy/TACE

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Table I (Continued).

Author	Year	N	Tumour Size Median (Range)	Dose	LC	OS	Toxicity	Comments
Jeong Y[30]	2018; retrospective	119	Median size=1.7 cm (0.8–6 cm)	30–60Gy in 3–4#	3-yr LC=97%	3-yr OS= 84%	2% acute ≥Grade 3 hepatic non-classic RILD; 6% worsening of CP≥2; 2% ≥Grade 3 late biliary strictures	LINAC based respiratory gated VMAT; no planned therapy/TACE
Liu et al[34]	2020; retrospective	59 (BCLC O/A) out of 96	Median size=3.8 cm (1.5–17 cm)	Median BED10 =86 Gy	FFLP at 18 months was 94% for BCLC 0/A	1-yr OS= 95% for BCLC O/A	7% increase in CP score >1 within 3 months of SBRT. Clinical toxicities grade ≥2-20%.	No UVA or MVA; no planned therapy/TACE
Yeung et al[35]	2019; retrospective	31	Median size=3.3 cm (1.3–5 cm)	45 Gy/3-5#	1-year LC= 94%	1-yr OS=84%	19% worsened CP score by>2 points; 32% > Grade 3 toxicities	Child-Pugh Class A or B, with small HCCs measuring ≤5 cm; On UVA, small tumour size predicted for improved overall survival (P = 0.01); no planned therapy/TACE
Mathew et al[28]	2020; retrospective	297; ineligible or recurrent/ residual after RFA/TACE; CP A/B/C=76/20/2	Median size=2.7cm (0.5–18.1cm)	27–60 Gy/ 3-6#	3-yr LRR=13%	3-yr OS= 39%	Worsening of CP score by ≥2 points three months after SBRT in 16%.	Liver transplant after downstaging post SBRT in 25 patients, CP A liver function, AFP ≤ 10 ng/mL, and ECOG status 0 significantly improved OS; no planned TACE
Kimura et al[31]	2020; prospective	36 (target 60; closed early due to poor accrual)	Median size=2.3 cm (1–5 cm)	40 Gy/5#	3-yr LC= 90%	3-yr OS=78%	≥Grade 3 toxicities= 11%	Previously untreated solitary HCC
Loi et al[32]	2020; retrospective	128 (BCLC Class A/B=31%/ 56%)	Median size= 3 cm (1.4–9.9 cm)	Median BED10 =103 Gy/ 3-10#; Range=30–75 Gy in 3–10 #	2-yr LC= 78%	2-yr OS=58% (whole cohort; separately NA)	Acute Grade 3 Toxicity- acute liver failure and ascites in 1 pt.	In BCLC stage A-B disease (n=112), LC associated with improved OS (median 30 months vs not reached, p=0.036)
Park et al[36]	2020; retrospective	290 (BCLC Class A=86%)	Median size=1.7 cm	Median 45 Gy in 3 –4# (Range 30–60 Gy/3-4 #)	5-yr LC= 91%	5-yr OS= 44.9%	≥Grade 3 hepatic toxicities=2.3%; 5.5% had decline in CP score of >2	MVA showed tumour size (< or > 3 cm) and serum albumin significantly associated with tumor LC.

Abbreviations: HCC, hepatocellular carcinoma; LC, local control; OS, overall survival; PVT, portal vein thrombosis; CP, Child-Pugh; LINAC, linear accelerator; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; RILD, radiation induced liver disease; FFLP, freedom from local progression; UVA, univariate analysis; MVA, multivariate analysis; VMAT, volumetric modulated arc therapy; AFP, alpha-fetoprotein; ECOG, Eastern Co-operative Oncology Group; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer classification; Gy, Gray; EQD2, equivalent dose in 2 Gy fractions; #, fractions; BED10, biologically effective dose with alpha/beta ratio of 10; m, month; yr, year.

Table 2 Comparison of SBRT with Radiofrequency Ablation (RFA) or Trans-Arterial Chemoembolization (TACE) in HCC

Author	Year	Number of Subjects (SBRT/RFA or TACE)	Dose (SBRT)	Study Design	Control Rates (SBRT/RFA)	Overall Survival	Comments
Kim et al[51]	2020	72 proton therapy/72 RFA	66 GyE/10#	Prospective Phase 3 randomised controlled trial-(Non-inferiority design)	2-year LPFS rate 95% (proton therapy)/ 84% (RFA) (90% CI 1.8–20.0; p <0.001)	2-year OS rates 92% (proton therapy)/91% (RFA)	First phase III randomized controlled trial of proton beam radiotherapy vs RFA in patients with recurrent small HCC
Kim et al[50]	2020	496 SBRT/1568 RFA	Median EQD2 (a/b of 10) 72 Gy (IQR 66–88 Gy); median BED$_{10}$ 86 Gy (IQR 79–106 Gy).	Retrospective with propensity score matching	3-yr cumulative local recurrence rate- 21%/28%, (p <0.001)	2-year Mortality Rate: 26% vs 19%, (p <0.001), before propensity matching	SBRT associated with superior LC in small tumors (≤3 cm) irrespective of location, large tumors located in the subphrenic region, and those that progressed after TACE
Su et al[55]	2020	167 (SBRT)/ 159 (TACE); 95/95 for PSM analysis	28–50 Gy/1-5#	Retrospective propensity matched analysis	3-yr/5-yr LC= 63%/57% (SBRT) vs 53%/ 37% (TACE) (p=0.0047)	3-yr OS= 65% vs 61% (p=0.29)	BCLC Stage A inoperable HCC; Cyberknife; On MVA, treatment (SBRT vs TACE) was a significant covariate associated with local and intrahepatic control (HR = 1.6; 95% CI: 1.03–2.47; P = 0.04; HR = 1.6; 95% CI: 1.13–2.29; P = 0.009)
Hara et al[44]	2019	143 SBRT/231 RFA	35–40 Gy/5# or 36–45 Gy/12-15#	Retrospective with propensity score matching (106 patients in each group)	Unmatched 3-year LRR= 5% (SBRT) (95% CI, 3–9) vs 13% (RFA), (95% CI, 10–16) (P < 0.01).	Matched 3-yr OS similar (69%; 95% CI, 58–78; and 70%; 95% CI, 59–79, respectively; P = 0.86).	SBRT- excellent LC and comparable OS in patients with well-compensated liver function.

(Continued)

Table 2 (Continued).

Author	Year	Number of Subjects (SBRT/RFA or TACE)	Dose (SBRT)	Study Design	Control Rates (SBRT/RFA)	Overall Survival	Comments
Parikh et al[43]	2018	32 SBRT/408 RFA	NR	Retrospective secondary analysis of SEER database-propensity score matched MVA	NR	Overall cohort- 3-yr OS significantly worse with SBRT (HR=1.8; 95% CI=1.15–2.82; p=0.01); in matched analysis, no difference in OS (HR=1.28; 95% CI=0.60–2.72; p=0.53)	SEER database study- older patients with higher co-morbidity burden in SBRT cohort; in matched analysis no difference in survival, 90-day hospitalisation and costs of treatment between RFA and SBRT.
Sapir et al[54]	2018	125 (SBRT)/84 (TACE)	Median BED=100 Gy/3-5#	Retrospective propensity matched analysis	2-year LC 91% (SBRT), 23% (TACE); The FFLP rates at 2 years were lower for patients after TACE than after SBRT (10.7% vs 26.9%, respectively), significantly favoring SBRT (HR=3.55, 95% CI= 1.94–6.52, P<0.001).	2-year OS-34.9% (SBRT), 54.9% (TACE); (HR 0.76, P=0.21)	Patients had 1–2 tumours, 7–11.6% patients had segmental portal vein thrombosis; institutional database; treated on LINAC based SBRT
Wahl et al[42]	2015	63 SBRT/161 RFA	Median doses 30–50 Gy/3-5# (Range 27 Gy-60Gy)	Retrospective institutional registry-based series with propensity score matching	2-year FFLP= 83.8% (SBRT)/80.2% (RFA)	2-year OS 46% (SBRT)/53% (RFA).	Increasing tumor size predicted for FFLP in patients treated with RFA (HR-1.54 per cm; P = 0.006), but not with SBRT (HR, 1.21 per cm; P =0.617).

Abbreviations: GyE, gray equivalent; Gy, Gray; #-fractions; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; TACE, trans arterial chemoembolization; LINAC, linear accelerator; LPFS, local progression free survival; FFLP, freedom from local progression; EQD2, equivalent dose in 2Gy per fraction; IQR, interquartile range; BED, biologically effective dose; BCLC, Barcelona Clinic Liver Cancer; MVA, multivariate analysis; LRR, local recurrence rate; SEER, Surveillance, Epidemiology and End-Results program; NR, not reported; HR, hazard ratio; CI, confidence interval.

SBRT was found to result in better outcomes if tumor size was 2–3 cm.[46]

Three large systematic reviews and meta-analyses have been reported recently comparing SBRT with RFA for early stage HCC, each of them including at least 2000 patients. Pan et al conducted a systematic review and meta-analysis of SBRT vs RFA in HCC, including 2783 patients and reported better local control of HCC using SBRT than RFA although overall survival was better with RFA.[47] This was attributed to differences in the underlying liver function in the patients selected for each of these modalities. Similarly, in a separate review by Lee et al, SBRT and RFA had similar local control rates for small early HCC's but RFA showed a benefit as far as overall survival odds ratio was concerned when compared to SBRT.[48] On the contrary, Wang et al in a review and meta-analysis of 7928 patients, reported better local control of HCC with SBRT than with RFA especially for slightly larger tumors (> 2cm) with equivalent overall survival outcomes and comparable toxicity.[49] In addition, a large multi-institutional retrospective study by Kim et al including 2064 patients reported significantly lower local recurrence rates with SBRT than with RFA in both the unmatched and propensity score matched cohorts.[50] SBRT was also associated with superior local control in small tumors ≤ 3 cm irrespective of location, large tumors in subphrenic location and those that progressed after TACE.

The only randomized controlled trial comparing radiation therapy to RFA has been reported recently from the National Cancer Centre, Korea comparing proton beam therapy (PBT) to RFA in small recurrent/residual HCC, using a non-inferiority design.[51] Patients with recurrent/residual HCC (size <3 cm, number ≤2) were randomly assigned to receive PBT or RFA according to Child-Pugh score and tumor stage. The 2-year LPFS rate with PBT vs RFA was 92.8% vs 83.2%, (90% CI 0.7–-18.4; p <0.001), meeting the criteria for non-inferiority. The 3- and 4-year LPFS rates for PBT were also non-inferior to those for RFA. Four-year survival was 75–77%, not significantly different in patients treated with either modality, when analyzed by intention to treat and per-protocol treatment. In this study, 26% of patients randomized to RFA crossed over to receive proton therapy, and 8% of patients randomized to proton therapy crossed over to receive RFA, demonstrating that factors such as tumor location and size make some

tumors more favorable for RFA (eg smaller tumors, and away from large vessels) or SBRT (eg larger tumors, away from luminal GI tissues).

Trans Arterial Chemoembolization (TACE)

Although TACE is the recommended treatment of choice for intermediate stage BCLC tumors, BCLC also endorses the concept of treatment migration so that TACE is recommended for early stage HCC patients who have recurred or who are not amenable for the recommended standard treatments. Several prospective series have reported outcomes of TACE in such early HCC with median survivals ranging from 54.2 months,[52] to 3-year survivals of 80.5%.[53] A propensity-score matched analysis of patients treated with TACE or SBRT was reported by Sapir et al with overall survival at 1 and 2 years of 75.3% and 54.9%, respectively, after TACE and 74.1% and 34.9% after SBRT, with no significant difference between treatment groups after adjustment for age, Child-Pugh score, baseline cirrhosis, liver transplantation, time from diagnosis of HCC, and thrombosis of minor branches of PV (HR 0.76, P=0.21)[54] (Table 2). A separate propensity-score matched analysis by Su et al in inoperable BCLC Stage A HCC also concluded that SBRT had better local control and intrahepatic control than TACE but showed comparable overall survival.[55] The accumulative 3- and 5-year OS rates were 65.1, and 62.8% in the SBRT group and 61.0, and 50.4% in the TACE group, respectively (P = 0.29). On multivariate analysis, treatment (SBRT vs TACE) was a significant covariate associated with local and intrahepatic control (HR = 1.59; 95% CI: 1.03–2.47; P = 0.04; HR = 1.61; 95% CI: 1.13–2.29; P = 0.009). Some studies have also mentioned that combined treatment with SBRT +TACE was more effective than TACE alone.[56] A recent preliminary analysis of a Phase III trial reported that use of SBRT after incomplete response to TACE/TAE as compared to further TACE/TAE itself resulted in significantly better local control (median not reached versus 8 months; p< 0.0002) in a single nodule, 5 cm or up to 3 nodules < 3 cm in diameter.[57] Other studies have reported similar control rates and survival in small HCC treated with SBRT alone or when combined with TACE also.[58,59] The interim analysis of a randomized controlled trial from the University of Loma Linda comparing proton therapy to TACE in patients eligible for liver transplant also reported encouraging trend towards improvement in local control

and (88% vs 45%, p=0.06) and progression-free survival (48% vs 31%, p=0.06) favoring the proton beam treatment group. 25% of the proton patients who underwent liver transplant showed a pathological complete response as compared to 10% of those who received TACE.[60]

Surgical Resection

Although no head-to-head randomized trial has been reported between surgical resection and SBRT, in a propensity score matched series for patients with small primary HCC with 1 or 2 nodules and Child-Pugh A cirrhosis, surgical resection and SBRT performed similarly in terms of overall survival, local control and toxicity.[61] However, in another study in patients with 1 to 3 small tumors (≤3 cm in diameter), surgical resection provided better long-term overall survival and disease-free survival.[62] Further study of these two modalities may be facilitated among patients who are medically ineligible for surgery or those who refuse surgery.

Future Directions

There is ample scope for use of SBRT in early stage HCC, both in the definitive setting as well as in the setting of bridge to transplant and generation of higher level of evidence is essential. Randomized controlled trials comparing SBRT to current standards of care ie to other liver-directed therapies, in this patient group are much needed and, in some cases, already ongoing.[63] Studies on clinically meaningful outcomes such as overall survival and progression-free survival, as well as cost-effectiveness of SBRT with regards to other liver-directed therapies are much needed. Another much less explored, but important, outcome is the quality of life of these patients who may struggle from symptoms of their HCC, underlying liver disease and/or treatment side effects, over a long time.[64]

The use of blood and imaging biomarkers in the selection of treatments for HCC is needed, beyond the use of Indocyanine green (ICG) dye clearance to assess liver function and guide dose schedules.[65] More integration of radiological biomarkers, even the use of functional imaging to select patients who will benefit from SBRT needs further study.

Disclosure

Dr Laura A. Dawson reports grants from Raysearch, outside the submitted work. The authors report no other conflicts of interest in this work.

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