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HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

Stereotactic Ablative Radiotherapy (SABR/SBRT) for Hepatocellular Carcinoma

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Abstract

Purpose of Review Liver-directed SABR (stereotactic ablative body radiotherapy) is emerging as an effective local therapy option for HCC (hepatocellular carcinoma). This review summarizes recent clinical progresses and proposes future directions.

Recent Findings SABR is an effective and safe, non-invasive local therapy option for HCC in the primary and salvage treatment settings, as well as a bridge to liver transplantation in selected patients. Randomized trials comparing SABR with other locoregional modalities are currently ongoing.

Summary Research efforts are being made toward better predicting normal tissue toxicity and tumor radiosensitivity for a tailored maximal safe treatment in HCC SABR. More recently, potential synergy with immunotherapies is of increasing interest in HCC.

Keywords Hepatocellular carcinoma · HCC · Liver SABR · Liver SBRT · Stereotactic ablative radiotherapy · Stereotactic body radiotherapy

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide [1]. The prognosis for HCC is poor, with overall ratio of mortality to incidence of 0.95 [1]. Despite its continual rise in incidence, there is still an unmet need for effective therapy. This has been largely due to the advanced stage at diagnosis, aggressive tumor biology, limited systemic therapy options, limitations of existing local therapies, and scarce donor organ availability for those eligible for transplant.

In the USA alone, more than 100,000 individuals are diagnosed with primary liver cancer each year, but less than 20–30% are candidates for curative resection due to either technical and or medical inoperability that is often complicated by underlying cirrhosis [2, 3]. Orthotopic liver transplantation has existed as a durable curative option with a 5-year survival rate exceeding 70% and recurrence rates of 15% [4], but is limited by donor availability and patient ineligibility. For the past decade, the multikinase inhibitor sorafenib has been the main systemic agents, providing a 2–3-month overall survival benefit in advanced HCC [5, 6]. Several non-operative locoregional therapy options exist, including radiofrequency ablation (RFA) and microwave ablation, cryoablation, transarterial embolization (TAE) (i.e., bland embolization), transarterial chemoembolization (TACE), radioembolization (Yttrium-90) and percutaneous ethanol injection (PEI). Most recently, a new external beam radiotherapy approach called stereotactic ablative body radiotherapy (SABR), (synonymous with stereotactic body radiation therapy or SBRT) has emerged as a promising modality.

This review highlights recent technological and clinical progress in liver-directed SABR for HCC, discusses ongoing controversies, and proposes future directions drawing from recent development in several domains including immunotherapy and imaging.

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Thermal Ablation and Embolization Therapy for HCC

For unresectable HCC, RFA and TAE/TACE are two commonly used local-regional therapies, with a wide variation in reported survival and local control rates. These therapies are

discussed in detail elsewhere [7, 8]. Long-term studies of RFA for selected patients show 5-year overall survival of over 50%, and local control rate ranging 59–97% for tumor size < 5 cm [7, 9–13]. The utility of RFA is limited by large (> 3 cm) tumor size and the heat sink effect when large blood vessels are near the tumor [8, 10, 11, 13, 14]. Rare toxicities associated with RFA include abscess formation and injury to surrounding tissues as a function of tumor location.

Embolization therapy takes advantage of the arterial-based perfusion of HCC and has shown survival advantage over supportive care for unresectable HCC in two landmark randomized trials and can induce substantial necrosis in HCC tumors [15, 16]. However, durable long-term tumor control for larger tumors is limited by revascularization within the tumor [8]. Toxicities associated with embolization include the post-embolization syndrome consisting of fever, nausea, abdominal pain, and ileus [17–19]. Sometimes, prolonged hospitalization is required to monitor the patients and to control pain [20].

Advancements in Radiotherapy and a Newly Established Role in HCC Treatment

Historically, conventionally fractionated external beam radiotherapy was limited to a largely palliative role in HCC, with low local control and overall survival rates. Attempts at improving local control with dose escalation were limited by the risk of radiation-induced liver disease (RILD), a potentially fatal syndrome of hepatomegaly and ascites [21, 22]. RILD is histopathologically characterized by veno-occlusive disease [23] and is seen more commonly with large-volume liver irradiation.

However, in the past decades, advancements in treatment planning, motion management, and image guidance have allowed for high precision focal irradiation with escalated radiation doses and low risk of toxicity. This success was founded in the principles of intracranial radiosurgery: potent/ablative radiation treatment delivered in one or a few treatments (hypofractionated, 5 or fewer treatments) with high precision and steep gradient of dose in the surrounding normal tissues [24]. Extracranial stereotactic radiotherapy is now commonly used in the clinic to treat a variety of cancers, including liver tumors. Results from various series of SABR for HCC are summarized in Table 1 [25–29, 30•].

The results from these series show SABR to be an effective treatment for HCC, with reasonable toxicity profiles. Andolino et al. reported on the use of SABR for 60 patients with HCC. Patients with CTP B cirrhosis were treated with more modest hypofractionation. Local control at 2 years using RECIST criteria was 90%. Twenty percent of patients developed progression of their CTP class within 3 months of treatment. Bujold and colleagues used a normal tissue complication probability approach to tailor prescription radiation doses, and showed high rates of local control with minimal toxicities. Takeda and colleagues reported on patients with HCC treated with SABR with or without preceding TACE. Local control at 3 years was high, and less than 10% of patients had an increase in their CTP score of 2 points.

Classic RILD is rarely seen with modern approaches to liver irradiation. However, "non-classic" RILD, a term largely encompassing any sign of liver injury or functional deterioration, can be observed [31]. Generally, measures of cirrhosis such as the CTP score can be used to select patients for different dose-fractionation treatment regimens, with more aggressive treatments for the patients with well-compensated cirrhosis. Cardenes and colleagues showed poor tolerance to SABR for patients with decompensated cirrhosis, and much of the published literature selects for patients with CTP A or CTP B cirrhotic states [25]. The primary consideration is sparing of non-tumor involved liver tissue [31, 32]. Integration of patient-specific functional imaging may further aid in the treatment planning process to limit radiation-induced toxicities [33–37]. Selection of dose-fractionation scheme for a given patient remains an active area of investigation.

Comparison with Other Local Therapies

To date, randomized clinical data directly comparing SABR with RFA for HCC is lacking. Investigators have reported on institutional results and analyzed the National Cancer Database in efforts to address this comparison.

A recent institutional series from the University of Michigan group compared outcomes of RFA and SABR for HCC. In this study, 224 inoperable, non-metastatic HCC patients who underwent RFA or SABR were included. One- and 2-year local control rate for tumors treated with RFA were 83.6% and 80.2% vs 97.4% and 83.8% for SABR [38•]. On multivariate analysis, treatment with RFA was associated with decreased local control (HR 3.84; $p = 0.002$). Importantly, tumor size influenced the difference in outcomes between treatment modalities. Among patients with tumors < 2 cm in size, no significant difference in local control was noted between SBRT and RFA, while among patients with tumor size ≥2 cm, RFA was associated with significantly inferior freedom from local progression (HR 3.35; $p = 0.025$). Results from these studies conflict with a report analyzing outcomes for SABR versus RFA from the National Cancer Database, in which patients treated with RFA had superior 5-year overall survival [39]. The authors used propensity matching to account for known confounders differing between the two groups. However, a multitude of patient-specific features are competing factors for survival in patients with HCC, and there are limitations in accounting for these variables and their impact on the outcome of survival in analysis of large sets of data such as this [40].

Table 1 Selected phase 1–2 prospective studies of SABR for hepatocellular carcinoma

References	Patients	Tumor Size	Doses/fractions	Median follow-up (mo)	Local control	Overall survival	Severe toxicity
Cardenes et al. 2010 [25]	(*N* = 17) CPA 35% CPB 65%	Median max diameter 4 cm (2–6)	CPA: 45–48 Gy/3fx CPB: 42 Gy/3fx and 40 Gy/5fx	24	100%	1 year 75% 2 years 60%	18% RILD (3 pts., all with CPB). No RT-related deaths
Andolino et al. 2011 [26]	(*N* = 60) CPA 60% CPB 40%	Median diameter 3.2 cm (1–6.5 cm)	CPA: 44 Gy/3fx CPB: 40 Gy/5fx	27	2 years 90%	Median 44 2 years 67%	0% ≥ 3 grade non-hematologic toxicity. 6% progressive liver dysfunction (4 pts., all pre-RT CPS ≥8)
Kang et al. 2012 [27]	(*N* = 50) CPA 87% CPB 13%	Median max dimension sum 29 mm (13–78 mm)	57 Gy/3fx	17	2 years 95%	2 years 69%	Grade 3: 6.4% Grade 4: 4.3%
Bujold et al. 2013 [28]	(*N* = 102) CPA 100%	Median tumor vol 117 cc (1.3–1913)	36 Gy/6fx	31	1 years 87%	Median 17 mo 1 years 55%	30% ≥ grade 3. 6.9% deaths possibly RT-related
Lasley et al. 2015 [29]	(*N* = 59) CPA 64% CPB 36%	≤ 6 cm. Median 33.6 cc (2–107.3)	CPA: 48 Gy/3fx CPB: 40 Gy/5fx	CPA 33 CPB 46	3 years: CPA 91% CPB 82%	Median: CPA 45 mo CPB 17 mo 2 years: CPA 72% CPB 33% 3 years: CPA 61% CPB 26%	Grade 3 or 4 hepatic enzymatic toxicity: CPA 11%, CPB 38%. 5% RILD (all with CPB and CPS ≥ 7)
Takeda et al. 2016 [30•]	(*N* = 90) CPA 91% CPB 9%	Median max diameter 2.3 cm (1–4)	40 Gy/5fx	42	3 years 96%	Median 55 mo 3 years 67%	8% Grade 3. No grade ≥ 4

CPA Child-Turcotte-Pugh A, *CPB* Child-Turcotte-Pugh B, *CPS* Child-Turcotte-Pugh Score

Similarly, Sapir et al. analyzed 209 patients who underwent either SABR or TACE for one to two tumors (2.3–2.9 cm) [41]. One- and 2-year LC favored SABR: 97% and 91%, respectively, for SABR and 47% and 23% for TACE (hazard ratio 66.5, $P < .001$), with higher grade 3+ toxicity with TACE (13%) vs SABR (8%).

SABR as a Bridging Therapy for Transplant Patients

The best bridging modality for orthotopic liver transplant is unclear. TACE is most commonly used [42, 43]. Several recently published works demonstrated SABR as an effective and safe option in selected patients as well [44–49]. Investigators from the Lahey Clinic presented preliminary results of a randomized phase 2 comparison of SABR and TACE prior to OLT at the American Society for Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI) meeting in 2016 [50•]. At the time of this interim report, 13 patients were treated with SABR and 16 with TACE. Retreatment rates were higher for the patients in the TACE arm, and toxicity and quality of life metrics including elimination of hospitalizations (required for TACE) appeared improved in the SABR arm.

Recognition of SABR as an Alternative for Treatment of Intermediate Stage HCC

In light of the literature evidence in favor of SABR thus far, the seventh Asia-Pacific Primary Liver Cancer Expert Meeting consensus statement recommended SABR as a safe and effective option [51]. In the USA, the recent NCCN (National Comprehensive Cancer Network) guideline included SABR as an alternative to ablation/embolization for unresectable or medically inoperable HCC [52].

Moderate Hypofractionation

A hallmark of SABR is the use of high-dose-per-fraction radiation (typically > 8 Gy/fraction) delivered in a short course (5 or fewer fractions). More moderately hypofractionated regimens (doses around 4 Gy per fraction, delivered over 15 or so fractions), planned delivered with the same guiding principles of SABR, can allow for delivery of very potent treatment courses when the beneficial effects of fractionation are most relevant, such as tumors abutting critical organs. Hong et al. reported on a phase II trial using proton therapy to treat HCC and intrahepatic cholangiocarcinomas in 15 fractions, with proton therapy [53]. Dose-per-fraction was 3.87 Gy or 4.5 Gy depending on tumor location. The median maximum tumor dimension was 5 cm for the HCC patients, and local control at 2 years was 94.8%.

Investigators from Loma Linda University reported interim results of a randomized trial comparing 15-fraction proton therapy (4.68 Gy per fraction) with TACE for patients with a new diagnosis of HCC [54]. Two-year progression-free survival was higher in the patients treated with proton therapy (48% versus 31%, $p = 0.06$). Patients treated with proton therapy also had fewer hospitalization days compared to patients treated with TACE.

The Problem of Metachronous Disease

In HCC management, a major challenge is development of disease at other sites in the liver. Even with partial hepatectomy for small tumors, liver recurrence rate exceeds 70% at 5 years [55]. Explanted liver specimens from patients who undergo OLT following successful local therapy with SABR show high rate of micrometastatic disease in untreated liver not detected on imaging [44, 45]. Indeed, progression free survival rate of < 50% is typically observed even when local control of > 85% is achieved with SABR. These results emphasize the need for better systemic therapies, the latter limited by the dysfunctional cirrhotic liver. However, immunotherapy may change this landscape.

SABR and Immunotherapy

In September of 2017, the PD-1 inhibitor nivolumab received accelerated FDA approval for advanced HCC after the phase I/II CheckMate-040 study showed an objective response rate of 15% (seven patients) including complete response in three, with disease control rate of 58%, and a median response duration of 15 months [56••]. More recently, the results from the KEYNOTE-224 study, a phase II trial for pembrolizumab in patients with advanced HCC, showed an objective response in 18 (17%) of 104 patients, with one (1%) complete and 17 (16%) partial responses, and stable disease in 46 (44%) patients [57•].

Radiation has been shown to favorably modulate the tumor immune microenvironment, cause a global change in immune stimulatory cytokine and chemokine profiles, promote a qualitative alteration in the T cell receptor repertoire, and enhance the tumoricidal phenotype of effector T cells [58•, 59•, 60, 61]. Synergistic effects of combined radiotherapy and immunotherapy, including checkpoint inhibitors, on local and distant tumor control have been described in various malignancies [58•]. The study of interaction between radiation and immunomodulating treatments is an area of active basic and translational cancer research.

Tumors can evade immune responses. Evidence in support of this in HCC has been recently demonstrated in resected human HCC where the immune suppressive checkpoint receptors PD-L1 and LAG-3 (Lymphocyte-activation gene 3) were found to be upregulated with a concomitant decrease in density of intratumoral CD8 T cells [62]. Recently, Friedman et al. and Kim et al. showed improved therapeutic efficacy when combining RT with a checkpoint inhibitor in murine models of HCC [63, 64].

If synergy between SABR (or radiation in general) and immune therapy is seen in HCC, this could lead to a paradigm shift in HCC treatment. Not only would improvement in locoregional control in primary treatment setting be possible through radiosensitising immunotherapy, but improved therapeutic efficacy of immunotherapy in metastatic setting also could be achieved via abscopal effect with SABR. To this end, there is currently an ongoing phase 1 trial for SABR with nivolumab and ipilimumab [65].

Conclusion

SABR has emerged as an effective and safe non-invasive local therapy option for HCC in the primary and salvage treatment setting, as well as a bridge to liver transplantation in selected patients. SABR has demonstrated a high rate of tumor control with differing side effect profile relative to other local therapies. Active work in better predicting normal tissue toxicity and tumor radiosensitivity to guide tailored maximal safe treatment is under way and potential synergy with immune checkpoint inhibition and possibly other immunotherapies is also an ongoing area of research.

Compliance with Ethical Standards

Conflict of Interest Jeffrey Meyer reports clinical trial support from Peregrine Pharmaceuticals, Inc. and DFINE, Inc. And he also reports royalties from UpToDate, Inc. Byung-Han Rhieu and Amol K. Narang each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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