Review

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Radiotherapy for HCC: Ready for prime time?

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Summary

Stereotactic body radiation therapy (SBRT) has an evolving role in the management of hepatocellular carcinoma (HCC), largely due to recent advances in imaging technology. Often utilized in situations where other locoregional therapies are not feasible, SBRT has been demonstrated to be an effective treatment that confers high rates of durable local control. However, there is limited evidence to firmly establish its place in the treatment paradigm for HCC. In this article, we review the current evidence and highlight specific considerations in the multiple settings where SBRT may be used, including for primary HCC treatment and bridging/downstaging, as well as exploring the potential for SBRT in the treatment of extrahepatic oligo-metastatic HCC.

Keywords: Stereotactic body radiation therapy; SBRT; Hepatocellular carcinoma; HCC; Protons.

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Background

Liver cancers are the sixth most common cancer by incidence and the fourth most common cause of cancer-related mortality worldwide.[1] Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for 75–85% of all cases.[1] The major risk factors for HCC include chronic hepatitis B virus or hepatitis C virus infection, alcohol use and non-alcoholic fatty liver disease.[2] The treatment paradigm of HCC is unique in that along with the technical and tumour factors, baseline liver function plays a strong role in dictating which modalities are most appropriate. As many patients have underlying liver disease at the time of treatment, this is a challenge which requires a multidisciplinary approach.

Patients with early stage HCC are eligible for curative treatments including surgical resection (partial hepatectomy or liver transplantation) or percutaneous ablation, most commonly in the form of radiofrequency ablation (RFA).[3–5] The Barcelona Clinic Liver Cancer (BCLC) classification system, is a useful criterion to guide treatment options. Resection or transplantation are preferred for early stage HCC. The Milan criteria, accepted for transplantation globally, includes patients with the following characteristics: ≤5 cm for a single lesion, or up to 3 lesions all measuring ≤3 cm, no gross vascular invasion and no nodal or distant metastases.[6] The San Francisco criteria is an expansion on this guideline, allowing for single lesions ≤6.5 cm or up to 3 lesions each measuring ≤4.5 cm, with a total tumour diameter of ≤8 cm.[7] For patients that are ineligible for surgical treatment, ablation can be utilized with curative intent, ideally in tumours less than 4 cm and away from major vessels.[8] Multifocal disease too numerous or too large for surgical or ablative therapy (BCLC stage B) may benefit from locoregional therapies such as transarterial chemoembolization (TACE). Patients with macrovascular invasion (BCLC stage C) are ineligible for the aforementioned therapies, and standard of care for these patients is treatment with systemic tyrosine kinase inhibitors such as sorafenib and lenvatinib. Second-line therapies are now also available, including the use of regorafenib and immunotherapies such as nivolumab.[9] The use of radiotherapy is not included in the BCLC staging treatment allocation schema, but there is a growing body of evidence which points towards radiotherapy as a potential tool for primary treatment or for bridging/downsizing purposes.

Radiotherapy in the treatment of hepatocellular carcinoma

Radiation treatment has been used to treat cancers since the early 20th century, when it was first applied to treat skin cancers.[10] Ionizing radiation produces double strand DNA breaks, leading to mutations which damage the DNA replication process. Due to impaired repair mechanisms, cancer cells are unable to replicate, leading to mitotic cell death. Historically, radiotherapy has been delivered in multiple treatments (fractions) over the course of weeks in 1.8–2 Gray (Gy) per fraction as a means of optimizing the therapeutic ratio (Fig. 1). The therapeutic ratio is a risk-benefit analysis applied in the delivery of radiotherapy to maximize the probability of tumour control while maintaining a low probability of

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toxicity. Achieving the optimal therapeutic ratio required to safely cure certain cancer histologies is not always possible, due to a higher resistance to ionizing radiation damage, or the presence of nearby critical organs.

In the case of primary liver tumours, the therapeutic ratio is narrowed because of concerns relating to radiation-induced liver disease (RILD), particularly in a population with known liver function impairment. In addition, other regional organs at risk, such as the stomach, duodenum and colon also represent dose-limiting structures. Prior to the improved conformality and image guidance of modern radiotherapy techniques, irradiation of liver malignancies required irradiation of large volumes of the liver, limiting doses to 30-40 Gy in conventional radiation (prolonged) fractionations, which led to tumour response rates of <30%.[11,12] With the increased precision of modern radiotherapy techniques, dose escalation studies have shown that ablative doses of radiation therapy can be delivered to portions of the liver safely and lead to improved tumour control rates of 67–68%.[13,14] The radiation dose tolerance of the liver is also dependent on the volume of the liver treated, with the maximum allowable safe dose being inversely correlated to the proportion of normal liver being treated. Beyond the therapeutic ratio, the efficacy of radiotherapy as the only primary treatment for HCC is reduced by the high propensity of regional and intrahepatic spread. Akin to partial hepatic resections for multifocal HCC, intrahepatic failures tend to be high even when the irradiated tumour is controlled locally. Radiotherapy has historically been used primarily for palliation of symptoms (*i.e.* whole liver radiotherapy) or in patients who fail initial standard accepted locoregional therapies (*i.e.* resection, transplant, RFA, TACE).

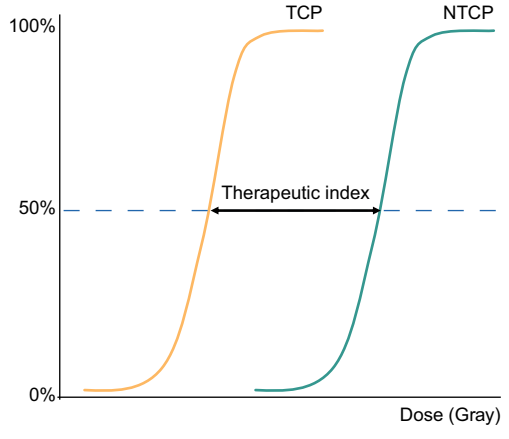

Fig. 1. Therapeutic ratio. Radiotherapy dose determination relies on the balance of maximizing TCP, while maintaining an acceptable NTCP. The therapeutic index represents the buffer of dose that exists between the tumour cells and normal tissue. This can vary depending on tumour histology and radiosensitivity of the nearby normal tissues. NTCP, normal tissue complication probability; TCP, tumour control probability.

Key points

Hepatocellular carcinoma (HCC) is a radiation sensitive tumour, and external beam radiation therapy, including stereotactic body radiation therapy (SBRT) has shown high rates of sustained local control in patients with varying stages of HCC. Overall prognosis relates to standard tumour, liver and patient prognostic factors.

The recent advances in radiotherapy for primary liver cancers are largely driven by the improvement in imaging technologies.

When properly delivered, SBRT can be a safe and effective local treatment for HCC, but it must be balanced by several factors including: baseline liver function, tumour volume and proximity to nearby luminal structures.

Stereotactic body radiation therapy

The introduction of intensity-modulated radiation therapy (IMRT) and improvements in image-guided radiation therapy have paved the way for greater precision and conformality of radiation delivery. Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative body radiotherapy (SABR), builds on the principles of the delivery of high doses per fraction (hypofractionation) using steep dose gradients and smaller margins of uncertainty (Fig. 2). In order to deliver this safely, image guidance and reduction of motion is required. The benefit of delivering high doses of radiation in a few fractions allows for a higher proportion of cell kill, while reducing the chance of tumour DNA repair or repopulation, effectively increasing the biologically effective dose. In addition, with the development of immunotherapy as a fourth pillar in cancer therapy, there is significant excitement in the radiation oncology community regarding the known immunogenic effects of radiotherapy. Radiation has been demonstrated to increase the recruitment of antigen presenting cells through the release of damage-associated molecular patterns following tumour cell death, as well as being shown to increase T-cell trafficking which can synergize with immune checkpoint inhibition.[15,16]

There are several unique challenges to using SBRT for liver tumours, including optimizing the therapeutic ratio (given inherent liver disease as a competing risk to HCC control), tumour visualization/targeting and motion management of the tumour throughout the duration of radiation treatment. To help achieve these objectives, utilization of specific imaging techniques is necessary to acquire images. One strategy that is commonly used includes the integration of multi-phasic MR imaging with baseline multiphasic CT scans acquired in the planning process. In addition, the motion of tumours can be restricted with active breath control (ABC), a process where patients are instructed to hold their breath for 15-20 second intervals, with the intent of only delivering radiation doses during

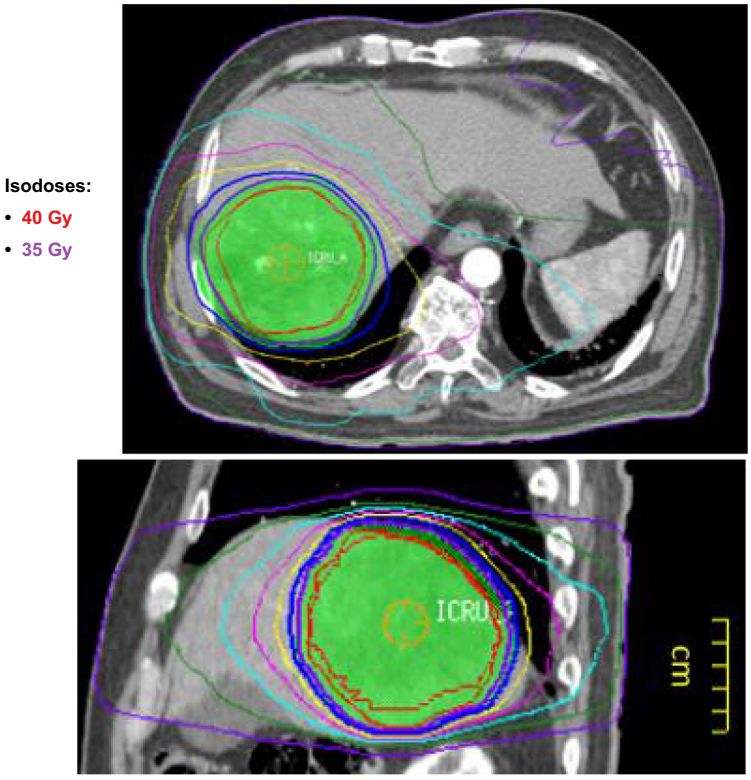

Fig. 2. Stereotactic body radiotherapy plan for primary hepatocellular carcinoma. Axial and saggital views of a stereotactic body radiation therapy plan for a 78-year old man with an 8 cm newly diagnosed hepatocellular carcinoma (290 cc) and compensated Hepatitis C-related cirrhosis (Child-Pugh A, platelet count 70,000). He was not a good candidate for resection, TACE or systemic therapies due to comorbidities including prior stroke, coronary artery disease, recent myocardial infarction, diabetes and hypertension. He was treated with 35 Gy in 5 fractions (purple contour that covered 95% of the planning target volume [green colorwash]).

these "on" breath-hold periods. Otherwise, acquisition of 4-dimensional CT scans (4D-CT), which account for the motion of the tumours throughout the respiratory cycle, can be used to prevent a geographic miss of the target. In addition to technical challenges, evaluating post-radiotherapy changes remains difficult, with heterogeneity in imaging interpretation as well as uncertainty regarding the correlations between radiology and pathology. Changes in the tumour and nearby irradiated liver can also lead to pseudo-progression, which should not be confused with true progression. This notwithstanding, in the absence of improved measures of response, durable local control is common with SBRT, which may be a more meaningful endpoint than actual response rate.[17]

Stereotactic body radiation therapy for primary hepatocellular carcinoma

For inoperable patients, SBRT is a flexible local treatment, allowing for treatment in a broad range of indications including large tumours, multifocal disease, presence of tumour vascular invasion and selected metastatic cases with isolated or oligo-metastases. There have been several prospective studies of patients with Child-Pugh (CP) A-B liver disease, reporting 2-year local control rates between 64% to 95%, and 2-year overall survival (OS) between 40% to 81% (Table 1).[18–26] In these studies, the doses of radiotherapy delivered ranged from 23 to 75 Gy in 3 to 6 fractions. The data is mixed with regards to radiation dose response, with some models suggesting dose escalation may improve local control, particularly in larger tumours,[27,28] while others have found that dose escalation is not necessary, possibly due to the radiosensitive nature of HCC.[29] These prospective studies included a range of patients with tumour vascular invasion from 0–55%,[18–26] and a few included patients with extrahepatic disease.[18,19,21,24]

Although the current standard of care for patients with HCC with vascular invasion is the use of a systemic tyrosine kinase inhibitors, the use of SBRT may be beneficial in this patient population. A phase II study reported by Yoon *et al.* randomized patients with CP-A status to receive sorafenib or TACE and radiotherapy (TACE-RT) with a primary endpoint of progression-free survival (PFS) at 12 weeks. The patients were treatment-naïve, with most patients having multifocal disease, and the median tumour diameter was 9.7 cm.[30] Patients who received TACE-RT were found to have an improved PFS at 12 weeks (86.7% *vs.* 34.3%,

Table 1. Selected prospective studies.

Study	Median follow-up, months (range)	CP score	Tumour vascular thrombosis	Extrahepatic disease	Median length or volume (range)	Dose/ fractionation	Acute grade 3+ GI or liver toxicity	Local control	Overall survival
Feng (2018) n = 90 [19]	37	A: 77% B: 23%	18%	19%	3 cm (0–13 cm)	23 Gy/5–60 Gy/5	7%	2-yr: 95%	n.a.
Kim (2018) n = 32 [20]	27 (12–55)	A: 88% B: 12%	0%	0%	2.1 cm (1.0–4.5 cm)	36 Gy/4–60 Gy/4	0%	2-yr: 81%	2-yr: 81%
Moon (2018) n = 30 [21]	12.7	A: 93% B: 7%	–	18%	22.5 cm^3 (2.8–145 cm^3)	27.5 Gy/5–45 Gy/3	7%	1-yr: 81%	1-yr: 36%
Takeda (2016) n = 90 [22]	41.7 (6.8–96.2)	A: 91% B: 9%	3%	0%	2.3 cm (1.0–4.0 cm)	35 Gy/5–40 Gy/5	11%	3-yr: 96%	3-yr: 67%
Lasley (2015) n = 59 [23]	CPA: 33.3 CPB: 46.3	A: 64% B: 36%	20%	0%	33.6 cm^3 (2–107 cm^3)	40 Gy/5–48 Gy/3	20%	3-yr: A: 91% B: 82%	3-yr: A: 61% B: 26%
Scorsetti (2015) n = 43 [24]	8 (3–43)	A: 53% B: 47%	20%	4%	4.8 cm (1–13 cm)	36 Gy/6–75 Gy/3	16%	1-yr: 86% 2-yr: 64%	1-yr: 78% 2-yr: 45%
Bujold (2013) n = 102 [18]	31.4	A: 100%	55%	12%	117 cm^3 (1–1,913 cm^3)	24 Gy/6–54 Gy/6	30%	1-yr: 87%	Median: 17 months
Kang (2012) n = 47 [25]	17 (6–38)	A: 87% B: 13%	11%	0%	2.9 cm (1.3–7.8 cm)	42 Gy/3–60 Gy/3	6.4%	2-yr: 95%	2-yr: 69%
Mendez–Romero (2006) n = 8 [26]	13 (1–31)	A: 63% B: 25%	38%	0%	3.5 cm (0.5–7.2 cm)	25 Gy/5–37.5 Gy/3	12.5%	1-yr: 75%	1-yr: 75% 2-yr: 40%

CP, Child-Pugh; GI, gastrointestinal.

p <0.001) and a longer median OS of 55 weeks compared to 43 weeks (p = 0.04).[30] It should also be noted that the combination of treatment was well tolerated with no patients in the TACE-RT cohort discontinuing therapy due to hepatic toxicities.[30] To further validate the use of radiotherapy in this setting, RTOG 1112 is a randomized phase III study investigating inoperable patients who are not candidates for other locoregional therapies including RFA and TACE. Patients are randomized to receive standard of care sorafenib or sequential SBRT followed by sorafenib with a primary endpoint of OS (NCT01730937).[31]

Stereotactic body radiation therapy for bridging or downsizing therapy

SBRT can also be used as local therapy to bridge patients awaiting liver transplantation as definitive therapy. Although there are no prospective studies examining the efficacy and safety of SBRT in this setting, particularly in direct comparison to more conventional treatments of RFA and TACE, based on retrospective data, SBRT appears to be a safe and effective alternative. An intention-to-treat analysis of a large cohort of patients receiving SBRT, RFA or TACE was performed by Saposachin *et al.*, demonstrating similar drop-out rates between the 3 groups (16.7% *vs.* 20.2% *vs.* 16.8%, p = 0.7) and no difference in 1, 3 and 5-year survival (5-year survival: 75% *vs.* 69% *vs.* 73%, p = 0.7).[32] In addition, with the high rates of local control observed with SBRT, it can potentially be used to downstage (or downsize) HCC to a volume within the Milan or San Francisco criteria, making patients eligible for liver transplant.

Stereotactic body radiation therapy for extrahepatic lesions

The recurrence pattern of HCC is predominantly intrahepatic following local therapy.[33] In cases of extrahepatic metastases, systemic therapy has long been the standard of care management strategy. This paradigm has been shifting to reintroduce local therapies in select patients with oligo-metastasis (generally defined as 5 or fewer sites of metastases), spurred by promising outcomes seen in the colorectal cancer literature. In addition to surgical resection, SBRT has been shown to be effective, demonstrating high rates of local control and improved PFS in prospective studies.[34,35] In a randomized phase II study of patients with oligometastases from mixed histologies (SABR-COMET), Palma *et al.* reported improved outcomes in PFS (12 *vs.* 6 months, p <0.001) and OS (41 *vs.* 27 months, p = 0.09) with the addition of SBRT to standard of care systemic therapy compared to systemic therapy alone.[36] Although phase III studies are needed, the data supporting an increased role for local therapies in oligometastatic disease are encouraging, particularly if advances in systemic therapies for patients with HCC, such as immunotherapies, continue to evolve. Fig. 3 is an example of a patient who received SBRT for an isolated retrocaval

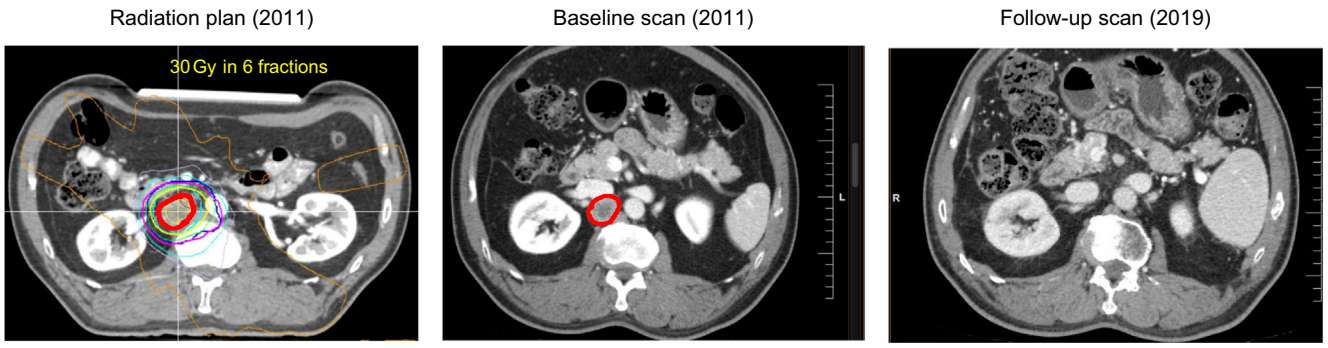

Fig. 3. Stereotactic body radiotherapy plan for oligometastasis. Example of a 60-year old man with hepatitis B who was treated in 2011 with stereotactic body radiation therapy (30 Gy in 6 fractions) to a 3.0 cm retrocaval lymph node (red contour). The patient has had a sustained complete response of the irradiated node, 8 years later.

lymph node metastasis from HCC, with a complete response that was maintained at the time of last imaging, 8 years following SBRT.

Particle beam radiation therapy

Particle beam radiotherapy represents another modality for delivering external beam radiotherapy, utilizing charged particles (*e.g.* protons or carbon ions) rather than the more conventionally used photons. The biggest distinction comes with the deposition of radiation dose, taking advantage of a phenomenon called the Bragg peak, which only occurs with heavier ionized particles. In essence, this allows for radiation to be concentrated at the desired target with no "exit dose", minimizing unwanted splash to surrounding organs at risk, which is particularly important for liver SBRT. Proton beam therapy is available and utilized in both clinical and research capacities in North America. Heavier carbon-ion particles are less widely available, but are being investigated around the world, and have been used to treat patients with HCC, with impressive 3-year and 5-year local control rates of 96% and 92% respectively.[37]

There have been several published prospective studies examining the efficacy and toxicity profiles of proton therapy. One single-institution randomized controlled trial conducted at Loma Linda compared the use of TACE and protons for transplant candidates (Milan or San Francisco criteria). In the interim analysis, there was no difference noted for OS, with a median survival of 30 months and 2-year OS of 59%.[38] However, there was a trend towards improved 2-year local control (88% *vs.* 45%, $p = 0.06$) and 2-year PFS (48% *vs.* 31%, $p = 0.06$) in the proton radiotherapy arm.[38] Though not reaching statistical significance, it was also noted that pathologic complete responses rates trended higher (25% *vs.* 10%), and the total hospitalization time as a result of therapy was significantly reduced for patients receiving proton treatment compared to those that received TACE (24 days *vs.* 166 days, $p < 0.001$).[38] Previous prospective studies have also demonstrated impressive local control rates approaching 95% at 2–3 years with low rates of radiation-related grade 3+ toxicities of 6–8%.[39,40] Taken together, proton beam therapy appears to be a safe and effective treatment modality. Further research is ongoing, with a randomized phase III study comparing OS in patients receiving either photon or proton-based radiotherapy (NCT03186898).[41]

Toxicities

As mentioned in this review, the efficacy of radiotherapy is constrained largely by nearby normal tissue dose tolerances. Two advantages of SBRT over conventional radiotherapy include lower total dose to adjacent organs and the rapid dose fall off which occurs specifically with this technique. Nonetheless, even with SBRT, potential liver-related toxicities include the sequelae associated with RILD: fatigue, abdominal pain, anicteric hepatomegaly, ascites and elevation of liver enzymes, which can typically develop 1-2 months following radiotherapy.[42] In addition to these findings, patients may also experience jaundice, thrombocytopenia and a change in their clotting factors. Reassuringly, examining the prospective literature, grade 3 or higher adverse events are rare, occurring in between 0–30% of cases (Table 1), with the majority of studies reporting rates of 12% or less. It should be noted that patients with a CP class of B7 or lower had a reduced risk of RILD compared to those with CP class B8 or higher.[23] In these more fragile patients with worse baseline liver function, radiation therapy is not recommended outside of the transplant setting or in clinical trials; if it is delivered, lower doses, such as 30 Gy in 5 fractions may help reduce the risk of toxicity.

Conclusions

The evolution of radiotherapy techniques in the treatment of HCC has raised new questions about its role in the prevailing treatment paradigm. Although HCC appears to be a relatively radiosensitive tumour, the recent advances in image guidance and technology have been key in enabling safer delivery of high-dose radiotherapy, paving the way for SBRT techniques. Both prospective

and retrospective studies demonstrate high rates of local control with limited hepatic and gastrointestinal toxicities. Similar to other local therapies aside from liver transplantation, SBRT is associated with relatively high rates of intrahepatic recurrences outside the irradiated field. Despite the (mostly single arm) studies demonstrating high local control post-SBRT, further phase III trials of SBRT are still needed to help carve out the exact role radiotherapy may play in the management of HCC. The ongoing RTOG 1112 study for inoperable patients who have relapsed after, or who are unsuitable for other conventional local therapies may provide answers for this specific patient population, while further trials are needed to explore this promising therapy in other situations.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2019.05.004.

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