

## Stereotactic Body Radiation Therapy in Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a primary liver cancer believed to originate from primary stem cells.<sup>[1]</sup> This cancer is increasing in its incidence likely due to the increase in the incidence of chronic hepatitis.<sup>[2]</sup> The treatment of choice is surgery and therefore every patient must undergo evaluation for surgery. However, most patients present in an inoperable stage<sup>[3]</sup> and the intent of treatment becomes palliative, an important goal of therapy being preserving the liver function for as long as possible. To achieve this, many liver-directed therapies (LDTs) have come up that can stall tumor progression. These include transarterial chemoembolization (TACE), transarterial radioembolization, radiofrequency ablation (RFA), intra-arterial chemotherapy, targeted drugs (sorafenib and lenvatinib), and IO drugs (nivolumab and pembrolizumab). In this therapeutic armamentarium, stereotactic body radiation therapy (SBRT) is an important addition. There is no specific experimental data that compare and contrast the above-mentioned modalities, and therefore, the treatment offered at most institutions is largely empirical and dependent on expertise and preferences of treating team. In this paper, we attempt to delineate the merits and relative strengths of SBRT for HCC.

SBRT is defined as a method of external beam radiotherapy that accurately delivers a high radiation dose to a target in one or few treatment fractions.<sup>[4]</sup> It is done by focusing high-energy radiation beams from multiple directions via specialized linear accelerators (TruBeam, Trilogy, Novalis, Edge, Synergy, Cyberknife, and others) that provide precise delivery of dose to prespecified target by shaping of beam perfectly on to the target and by checking for even minor errors in the position of target at the time of radiation delivery by image guidance technology. Typically, SBRT treatment sessions are 3–10 in number, and the dose delivered in each fraction is 5 Gy or more depending on the best compromise reached between radiation dose to the target and normal tissues on the computerized planning system. Smaller the tumor, larger the dose that can be delivered into it without compromising liver function. The aim is to ablate the tumor without damage to the functioning liver tissue.

Let us examine the role of SBRT in various clinical situations with HCC.

### For Small Lesions

Small lesions are typically those that are <3 cm in size. While RFA is a valuable modality in such cases, SBRT has been reported to provide equivalent results in some studies<sup>[5]</sup> and is deemed inferior in others.<sup>[6]</sup> In general, we can expect 90%–100% local control (LC), which is equivalent to RFA.

LC may be lesser for patients with worse baseline liver function, such as Child–Turcotte–Pugh (CP)-B patients. The same is likely related to the lower radiation dose delivered in order to decrease the risk of radiation-induced liver disease (RILD) in these patients.<sup>[7–10]</sup> However, RFA studies report more long-term data which are scarce with regard to SBRT, being a relatively newer modality. Wahl *et al.* published a retrospective study and reported a comparison between SBRT and RFA. They reported that the results tilt in favor of SBRT once the size increases above 2 cm.<sup>[5]</sup> SBRT seems to be an equivalent modality to RFA at sizes below that and will be preferable in lesions close to blood vessels, subcapsular location, the nonspherical shape of borderline size, or diffuse lesions with no clear margins, all of which are tumor-related factors that predict higher rates of failure with RFA.<sup>[11]</sup>

### Stereotactic Body Radiation Therapy in Locally Advanced Hepatocellular Carcinoma

In 2006, Méndez Romero *et al.* reported the first prospective data on liver SBRT for HCC demonstrating LC and safety in 11 lesions. LC rates at 1 and 2 years for the whole group (which included liver metastases) were 94% and 82%, 1 CP-B patient experienced RILD-related death.<sup>[12]</sup> Kang *et al.* reported a prospective phase II trial in 56 HCC lesions, showing 2-year LC of 95% after SBRT. Grade  $\geq 3$  toxicity was reported at 4.3%.<sup>[13]</sup> Bujold *et al.*<sup>[14]</sup> reported an analysis of 102 patients with HCC (CP-A 100%) and reported a 1-year LC of 87%. The lesions treated were a median diameter of 7.2 cm (range: 1.4–23.1 cm). Hepatotoxicity was seen in 30% of patients. Seven percent of deaths were possibly related to RILD. Culleton *et al.*<sup>[15]</sup> published a prospective study on 29 patients with HCC with CP-B7 and above (69% B7). Portal venous tumor thrombus (PVTT) was present in 76%. They reported LC of 65% at 1 year, which is lower than previous studies and a median OS of 8 months. Ten patients had locally advanced HCC that was in primarily life-threatening stage, e.g., PVTT. They reported that patients with CP-B7 have a significantly higher median OS of 9.9 months versus 2.8 months in CP-B8 + patients ( $P = 0.011$ ). They also showed that CP  $\geq B8$  and alpha fetoprotein >4491 ng/mL were poor prognostic factors. All these suggest that patients with CP-B8 + should not be treated with SBRT as it may not improve outcomes. They reported a higher rate of hepatotoxicity with a CP-score increase of 2 or greater (CP + 2) of 63% at 3 months. These studies show that patients often referred for SBRT are large, pretreated with other LDTs, often having PVTT and therefore patients need to be chosen wisely based on size and CP score balanced with the expected goal of treatment

(for example, in some very large-sized cases, treating only PVTT can yield good outcomes with a possibly lower risk of hepatotoxicity). Furthermore, the presence of so many adverse factors compounded with pretreatment with other LDTs may confound LC, intrahepatic control, and hepatotoxicity reporting.<sup>[13,14,16]</sup>

### **Stereotactic Body Radiation Therapy Along with Transarterial Chemoembolization**

This deserves a special mention because the most common pretreatment for HCC patients referred for SBRT is TACE with 40%–100% patients having received the same.<sup>[13–16]</sup> Huo and Eslick reported a meta-analysis of 17 trials with a total of 25 trials (11 RCTs) involving 2577 patients. TACE plus RT showed significantly better 1-year survival and complete response rate compared with TACE alone. The survival benefit progressively increased for 2-, 3-, 4-, and 5-year survival. The authors concluded that for an inoperable HCC patient, TACE plus RT was more therapeutically beneficial than TACE alone.<sup>[17]</sup> Since there are no set guidelines, SBRT and TACE are either utilized together in a planned manner or only as salvage after TACE. Buckstein *et al.* reported a retrospective review of outcomes in 103 patients receiving SBRT within 2 years following TACE to a target lesion. Fifty-two patients had planned adjuvant SBRT after TACE, and the remainder had salvage SBRT with no significant differences between the characteristics of the two groups. Planned TACE + SBRT reported more CR rates than salvage SBRT (79.6% vs. 43.5%,  $P = 0.006$ ). One-year survival for planned TACE SBRT was 70.8% versus 61.5% for salvage ( $P = 0.052$ ). They concluded that TACE + SBRT might achieve superior outcomes than salvage in view of superior overall response and CR rates.<sup>[18]</sup>

SBRT for PVTT: Incidence of PVTT in cases of HCC can be as high as 40%.<sup>[19]</sup> The presence of the same portends a poor prognosis. Patients with PVTT generally are not suitable for TACE as the probability of hepatic decompensation with embolization is quite high in them. BCLC staging and treatment algorithm advises only the use of sorafenib for these patients who fall in BCLC Stage C. Lin *et al.* reported 79% response rates for PVTT in their prospective study on 43 patients who received RT for PVTT.<sup>[20]</sup> They also reported survival benefit for those who responded. In another study<sup>[21]</sup> of 41 patients treated with SBRT for PVTT and/or inferior vena cava thrombus, the authors reported 36.6% complete response rates and 39% partial response rates of PVTT. They too reported survival benefit to patients who responded. Li *et al.* recently reported results on 108 pairs of patients with PVTT who were paired based on propensity score matching. These pairs compared patients receiving TACE + SBRT versus TACE alone. The median survival time was 10.9 versus 4.1 months ( $P < 0.001$ ) in all patients, 12.5 versus 4.4 months ( $P = 0.002$ ) in patients with PVTT involving the

right/left portal vein, and 8.9 versus 4.0 months ( $P < 0.001$ ) in patients with PVTT involving the main portal vein trunk. At uni- and multivariate analysis, SBRT + TACE as treatment, maximum lesion diameter and PVTT in the main trunk were the independent prognostic factors for survival. It is reported that TACE and SBRT yield better outcomes when planned in succession than as salvage;<sup>[18]</sup> however, which modality should be employed first is a matter of debate. A randomized study by Kang *et al.*<sup>[22]</sup> where they randomized patients into SBRT followed by TACE (Group A), TACE followed SBRT (Group B), and SBRT alone (Group C) reported overall response rate of 87.1%. Between Groups A and B, the differences in the response rate, survival rate,  $\alpha$ -fetoprotein level restoration rate, and rate of improvement of abdominal distention and discomfort were not statistically significant ( $P > 0.05$ ). However, these rates for Groups A and B were significantly higher compared to those of Group C ( $P < 0.05$ ). Importantly, deterioration of liver function in Group A was significantly lower compared to that in Group B ( $P < 0.05$ ). The authors reported that compared to SBRT followed by TACE versus SBRT alone, TACE followed by SBRT may exert a negative effect on liver function.<sup>[22]</sup> Yoon *et al.* reported the results of the START trial in 2018. They randomized 90 CP-A patients with liver-confined HCC and PVTT to either sorafenib or TACE followed by RT (TACE-RT). They reported results of TACE-RT versus sorafenib in 12-week progression-free survival (87% vs. 34%), 24-week radiographic response rate (33% vs. 2%), median time to progression (31 vs. 12 weeks), and OS (55 vs. 43 months). In this disease with an overall grim prognosis, these results are quite encouraging toward a strong consideration for SBRT in multimodality treatment of HCC.

### **Stereotactic Body Radiation Therapy as a Bridge to Transplant**

TACE, RFA, and SBRT are all utilized as a bridge to transplantation. A retrospective cohort analysis at Princess Margaret Hospital reported no survival difference between these three modalities in patients treated as a bridge to transplantation.<sup>[23]</sup> While only 24% and 36% of TACE and SBRT patients met the Milan criteria, 88% of RFA patients met these criteria. A recent study presented at the 2017 GI Cancers Symposium reported outcomes of prospective comparison between SBRT and TACE for transplant patients.<sup>[24]</sup> Time to retreatment was their primary endpoint, which is important in this clinical setting. They reported 40% rates of retreatment in TACE arm compared to none in SBRT arm. One of the secondary endpoints reported was toxicity that was found to be more in the TACE group.

All the clinical data shared above suggest that SBRT is an effective local therapy for parenchymal lesions as well as PVTT. The combination of TACE and SBRT becomes relatively more effective with higher survival rates. In the presence of PVTT, SBRT should precede

TACE. This approach is rational and understandable because recanalization post-SBRT can improve outcomes post-TACE by providing better perfusion of normal liver when the hepatic artery is embolized. It is also evident that in the light of recent results of START trial,<sup>[22]</sup> TACE and radiation therapy must be strongly considered for better outcomes as compared with sorafenib alone.

SBRT, which is newer modality, is different from other LDTs in being biological in its approach, because it targets the ultrastructural DNA damage and change of tumor microenvironment. It does not rely on physical damage to the tumor and therefore is effective in areas close to blood vessels, liver capsule, in lesions that are irregular or not well demarcated, in lesions with PVTT, and in relatively larger lesions (>2 cm). SBRT can also be effective in unresectable lesions, as a bridge therapy, along with TACE (before or after depending upon the presence of PVTT) for superior outcomes. For PVTT, it is a highly effective modality that improves survival, especially in patients with better hepatic reserves. It is now prudent to perform and report randomized trials with LDTs for better understanding of their relative merits.

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