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STEREOTACTIC BODY RADIOTHERAPY (SBRT):CHANGING TRENDS IN THE MANAGEMENT OF UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

Suhag V*[1], Sunita BS[2], Vats P[3], Pandya T[4], Lohia N[5], Singh VK[6], Tiwari M[7]

[1]MD DNB Radiation Oncology, Prof & Head Radiation Oncology, Command Hospital (SC), Pune, India [2]MD DNB Pathology, Professor Pathology, Armed Forces Medical College, Pune-411040, India [3]MBBS, DNB Radiation Oncology (Resident), Army Hospital (R&R), Delhi Cantt, Delhi-110010, India [4]DNB Radiation Oncology (Gd Specialist), Command Hospital (EC), Kolkata, India

[5]DNB Radiation Oncology (Gd Specialist), Command Hospital (CC), Lucknow, India

[6]MBBS, DNB Radiation Oncology (Resident), Army Hospital (R&R), Delhi Cantt, Delhi-110010, India [7]MBBS, DNB Radiation Oncology (Resident), Army Hospital (R&R), Delhi Cantt, Delhi-110010, India

ABSTRACT

Hepatocellular carcinoma (HCC) is considered as an aggressive liver tumor with a poor 5-year survival rate. Many HCCs are not amenable to surgical resection, because of tumor size, location or due to underlying poor liver function because HCC almost always develop in chronically inflamed livers. Depending on the extent of disease and comorbidities, multiple liver-directed therapy (LDT) options exist for the treatment of HCC. Historically, the use of external-beam radiotherapy (EBRT) for HCC been limited by toxicity to the uninvolved liver and surrounding structures. Advances in RT have improved dose conformity to the tumor and facilitated dose escalation, a key contributor to improved HCC radiation treatment outcomes. These advancements in radiation oncology have led to the emergence of stereotactic body radiation therapy (SBRT) as a promising LDT, which delivers high doses of radiation with a steep dose gradient to maximize local tumor control and minimize radiation-induced treatment toxicity. This review will enlighten the primary physicians and oncology care providers about the promising and evolving role of RT in various stages of HCC.

Key words: Hepatocellular carcinoma (HCC)–Liver-directed therapies (LDT)–Radiotherapy (RT)–stereotactic body radiation therapy (SBRT).

1 INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common gastrointestinal malignancy and the fourth leading cause of cancer-related death with a rising trend worldwide. The majority of patients with HCC have underlying chronic liver disease caused by viral hepatitis and/or fatty liver disease. [1, 2] Surgery remains the gold standard for curative treatment and includes either a partial hepatectomy or liver transplantation. Transplantation is associated with an 84% 2-year overall survival (OS); however, only 15% to 30% are candidates due to tumor extent and underlying liver dysfunction. The majority of patients diagnosed with HCC present in intermediate or advanced tumour stages, are not eligible for radical curative therapy, and median survival for such patients is less than one year. [2, 3] For these patients, other liver-directed therapies (LDTs) are evaluated in a multidisciplinary setting with various treatment intents, such as bridge-to-transplant, definitive/curative treatment, and/or palliation.Most patients with nonmetastatic HCC receive one or more of the following LDT over the course of their treatment: radiofrequency ablation (RFA), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and external beam radiotherapy (RT).

* Corresponding author.Suhag V

There appears to be significant disparity in care of unresectable HCC patients with significant underutilization of cancer-directed therapies. [1, 4] In a recent review by Eggert T[5] (2017) on role of LDT in unresectable HCC, it was highlighted that (1) RFA is currently the preferred treatment for patients with tumor burden restricted to the liver and who are not eligible for surgical resection; (2) TACE is utilized in patients who are not eligible for RFA because of tumor location and/or number of tumor lesions; (3) SIRT (selective internal radiation therapy) might improve treatment responses achieved by TACE and is feasible in patients with portal vein thrombosis; (4) New radiation therapy treatment modalities such as SBRT and proton beam therapy show promising results for local tumor control; (5) Sorafenib remains the first line systemic treatment option after several large clinical trials have failed to show superiority of other molecular targeted therapies in HCC patients. [5, 6] These facts have been summarized as Algorithm in Figure 1 . Liver SBRT is a safe and effective treatment even in the setting of prior liver-directed surgical and ablative therapies. [7]

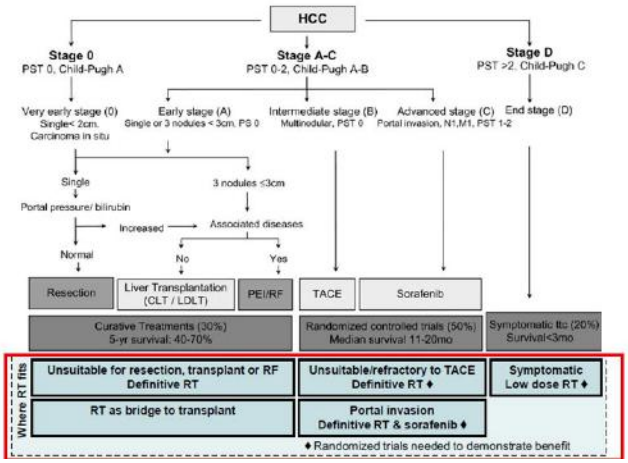

Figure 1. Algorithmshowing role of SBRT in HCC

2 EVOLVING ROLE OF RT:

Historically, the role of RT for the treatment of HCC has been limited because of the low tolerance of the whole liver to RT and the risk of radiation-induced liver disease (RILD). [8] The most important challenge in EBRT for HCC includes delivering a sufficiently high dose of radiation to achieve tumor control in an organ that is highly sensitive to radiation and that moves substantially with breathing, making target localization very difficult. [2] With the introduction of 3-dimensional conformal radiotherapy (3DCRT), the delivery of conformal partial liver RT allows for safe dose escalation with acceptable morbidity. In addition, further development of radiotherapy techniques, including intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), has expanded the indication of RT for the treatment of HCC from a palliative to a curative-intent aim. [8] SBRT delivers highly conformal dose distributions with a rapid dose drop off that offers the ability to spare large portions of the liver while simultaneously allowing for dose escalation with ablative potential within the tumor. Stereotactic body RT presents an alternative and/or combined modality to use with other LDTs. [1] It is expected that quality of life and overall survival would benefit from SBRT for primary tumours. Another potential advantage of SBRT is its ability to increase tumor immunogenicity, while also having less of an immunosuppressive effect on the patient, as compared to conventionally fractionated RT. In doing so, SBRT may potentiate the effects of immune therapy when the two treatments are combined, thus improving therapeutic outcomes. Role of Radiotherapy in management of HCC is increasingly being incorporated in the standard universal guidelines. [2, 9]

RT as a Potential Radical Treatment in Early and Intermediate Stage HCC:

Poor underlying liver function and/or comorbidities render the majority of HCC patients inoperable. Patients with small tumors (e.g., <3 cm) are best suited to RFA or local ablative treatments. Although TACE is the standard recommended treatment for patients unsuitable for RFA, TACE is not a curative treatment option in most cases. RT alone (without TACE) has been used with curative intent to treat early stage HCC, with promising outcomes. [10] SBRT is an emerging modality for definitive treatment of early HCC. Moore and colleagues [11] (2017) conducted a retrospective study of 23 early stage yet unoperable HCC patients treated with SBRT. The median tumor volume was 12.7cm^3 (range, 2.2-53.6 cm^3). Treatment was well tolerated. SBRT was a bridge to transplantation in 16 patients and 11 were transplanted. No surgical difficulties or complications were reported following SBRT, and none of the transplanted patients had local progression before transplantation. The median prescribed dose to the tumor was 54Gy and the median dose to the uninvolved liver was 6.0Gy. There was no SBRT-related mortality. Liver explant post SBRT revealed pathological complete response in 3(27.3%), pathological partial response in 6(54.5%), and pathological stable disease in 2(18.2%) tumors. The authors concluded that SBRT is safe and effective as definitive management of early stage inoperable HCC.SBRT with optional TACE can be effective against solitary HCC in treatment-naive, intrahepatic failure, residual disease, and recurrent settings, taking advantage of its distinctive characteristics. [12]There is evidence to show that SBRT for HCC is well-tolerated even in patients with advanced cirrhosis and prior liver-directed treatment and provides excellent local control (LC) even for larger lesions that cannot be controlled with radiofrequency ablation. LC with SBRT compares favorably to other LDTs. [13, 14]

SBRT in combination with TACE:

In patients with intermediate HCC, TACE is the treatment of choice. Importantly, many patients are treated with several TACE sessions to achieve a good local tumor control and in some patients further transarterial approaches may be limited due to impaired vascular architecture after

several embolization procedures. [15] In these patients sorafenib is standardly used by applying the concept of treatment stage migration. However, sorafenib is associated with several adverse events such as diarrhea and hand-foot syndrome which may limit treatment duration and therefore efficacy. SBRT is a promising noninvasive treatment with acceptable toxicity not only for primary HCC but also for recurrent or residual HCC patients after TACE. There are a number of advantages to combining SBRT with TACE. TACE can shrink tumors, thus creating a smaller treatment volume for SBRT. The combination of the two treatments allows for ablation of vascular components of the tumor with TACE, while the poorly vascularized, necrotic portions can be targeted by SBRT. Finally, SBRT can be used to recanalize tumors with arterial or portal vein thromboses, rendering TACE more effective. [2, 9] In one such study, Yao et al [9] evaluated the efficacy and toxicity of SBRT in 33 patients with 63 lesions of recurrent or residual HCC after TACE. A total dose of 39-45 Gy/3-5 fractions was delivered with an objective response rate of 84.8% at 6 months. The overall survival rate was 87.9%, 75.8%, 57.6%, and 45.5% at 6, 12, 18, and 24 months, respectively. Median overall survival was 19 months. At 3 months, AFP decreased by more than 75% in 51.5% of patients (17/33). Eight patients (24.2%) had grade 1-2 transient fatigue, and 11 patients (33.3%) had grade 1-2 gastrointestinal reactions within 1 month. The authors concluded that SBRT is a promising noninvasive and palliative treatment with acceptable toxicity for recurrent or residual HCC after TACE. Buckstein and colleagues [16] (2018) retrospectively reviewed 133 patients receiving SBRT within 2 years following DEB (drug eluting bead)-TACE to a target lesion. Fifty-two patients had planned adjuvant SBRT after DEB-TACE and the remainder had salvage SBRT. Of 95 patients with follow-up imaging, 59 (62.1%) had a complete response and 25 (26.3%) had a partial response (PR). More patients achieved CR (79.6% vs.43.5%) with planned TACE + SBRT than salvage (P=0.006). LC was 91% and 89% at 1 and 2 years, respectively. One-year survival for planned DEB-TACE SBRT was 70.8% vs. 61.5% for salvage (P=0.052). This study showed that combination TACE + SBRT achieves high OR and LC rates and might achieve superior outcomes than salvage. This strategy might be particularly effective as a bridge to transplant.

Jacob et al [17] conducted a retrospective study to measure survival in patients with HCC of $\geq$ 3 cm treated with adjuvant stereotactic body radiotherapy (SBRT) following TACE. Outcomes in patients treated with TACE alone (n = 124) were compared with outcomes in those treated with TACE + SBRT (n = 37). Local recurrence was significantly decreased in the TACE + SBRT group (10.8%) in comparison with the TACE-only group (25.8%) (P = 0.04). After censoring for liver transplantation, overall survival was found to be significantly increased in the TACE + SBRT group compared with the TACE-only group (33 months and 20 months, respectively; P = 0.02). This study confirmed that in patients with HCC tumours of $\geq$ 3 cm, treatment with TACE + SBRT provides a survival advantage over treatment with only TACE. Su and colleagues [18] (2017) retrospectively compared the outcome and evaluat the prognostic factors of stereotactic body radiation therapy (SBRT) alone or as an adjunct to transarterial embolization (TAE) or TACE in the treatment of HCC >5 cm. In this study, 77 patients received SBRT followed by TAE or TACE (TAE/TACE + SBRT group) and 50 patients received SBRT alone (SBRT group). Median overall survival (OS) in the TAE/TACE + SBRT group was 42.0 months versus 21.0 months in the SBRT group. The 1-, 3- and 5-year OS was 75.5, 50.8, and 46.9 % in the TAE/TACE + SBRT group and was 62.4, 32.9, and 32.9 % in the SBRT group, respectively (P = 0.047). The 1-, 3- and 5-year distant metastasis-free survival (DMFS) was 66.3, 44.3, and 40.6 % in the TAE/TACE + SBRT group and was 56.8, 26.1, and 17.4 % in the SBRT group, respectively (P = 0.049). The authors concluded that SBRT combined with TAE/TACE may be an effective complementary treatment approach for HCC >5 cm in diameter.

RT as a Bridge to Liver Transplantation:

Use of local therapies to halt progression of HCC in patients on waiting lists for liver transplantation may allow more patients to remain eligible for transplantation. [5, 19] Alternatively, for patients with HCC that exceeds size guidelines for transplantation, therapies are sometimes given with the goal of downstaging the HCC so that it falls within transplant guidelines (e.g., the Milan criteria). Traditionally, transcatheter arterial chemoembolization (TACE) and RFA have been the most commonly used bridging or downstaging treatments. However, there is emerging interest in the use of RT, specifically SBRT, as a bridging therapy, especially for patients not well suited to RFA or TACE. [10]

Sapisochin et al [20] (2017) compared the safety and efficacy of SBRT with TACE and RFA as a bridge to liver transplantation in a large cohort of 379 patients with HCC treated with either SBRT (n=36), TACE (n=99) or RFA (n=244). 30 patients were transplanted in the SBRT group, 79 in the TACE group and 203 in the RFA group. The 1-, 3- and 5-year survival from the time of transplant was 83%, 75% and 75% in the SBRT group vs. 96%, 75% and 69% in the TACE group, and 95%, 81% and 73% in the RFA group, p=0.7.The authors concluded that SBRT can be safely utilized as a bridge to LT in patients with HCC, as an alternative to conventional bridging therapies.

SBRT in HCC with portal vein tumor thrombosis (PVTT):

SBRT combined with TACE for advanced HCC with PVTT has been shown to be feasible treatment modalities with minimal side effects in selected patients with primary HCC. [21]Matsuo Y [22] (2016)evaluated the efficacy of stereotactic body radiotherapy (SBRT) compared with 3DCRT in HCC patients with thrombosis. Forty-three patients with portal vein tumor thrombosis (PVTT)/inferior vena cava tumor thrombosis (IVCTT) treated with SBRT (27 with CyberKnife (CK) and 16 with TrueBeam (TB)) , and 54 treated with 3DCRT were evaluated. Dosimetric parameters, response to radiotherapy (RT) and survival outcomes were compared in total SBRT vs. 3DCRT, CK vs.

3DCRT and TB vs. 3DCRT, respectively. The tumor response rates were 67%, 70%, 62% and 46%, respectively (P = 0.04, P = 0.04, P = 0.25). The 1-year overall survival rates were 49.3%, 56.7%, 38.1% and 29.3%, respectively (P = 0.02, P = 0.02, P = 0.30), and the 1-year local progression rates were 20.4%, 21.9%, 18.8% and 43.6%, respectively (P = 0.01, P = 0.04, P = 0.10). This study showed that SBRT may have the potential to be the standard RT technique for the treatment of PVTT/IVCTT. (

Emerging role of Particle beam therapy:

Charged particle therapy such as proton and carbon ion therapy is showing initial promising results over photon based EBRT. The distinctive biophysical attributes of charged particles, namely the lack of exit dose along the beam path beyond the tumor and higher biological effectiveness, confer unique advantages to charged particle therapy over photon radiotherapy in the treatment of HCC providing in-field local control rates exceeding 80%. Taken together with the gratifying 5-year overall survival rates of nearly 25%, these results make a compelling argument for the use of proton radiotherapy as a viable liver-directed treatment option for patients with localized HCCs who are unable to undergo surgical resection or transplantation. Defining a definitive role for charged particle therapy in the treatment of HCC is, however, hampered by the relative scarcity of treatment facilities and the lack of randomized trials demonstrating the clinical benefit of charged particle therapy over other modalities for treating HCC. In scenarios such as major portal venous thrombosis, where treatment with other liver-directed therapies is a relative contraindication, proton radiotherapy is likely to offer a unique definitive treatment option that results in resolution of thrombosis and reconsideration of previously nonviable therapeutic options. [23] [24, 25]

3 CONCLUSION:

HCC is a common cause of cancer-related death worldwide. Treating HCC is challenging and complex because of the natural history of the disease itself and the prevalence of advanced comorbidities seen in patients with HCC. Patients who are ineligible for liver transplant or partial hepatectomy have many different LDT options. Choosing an option that maximizes clinical benefits and limits risk of toxicity is essential. SBRT has emerged as an effective LDT for properly selected patients with HCC having excellent rates of LC and minimal treatment associated morbidity. Specifically, radiation plays a role for lesions unsuitable for other local therapies, for larger lesions in which TACE is less effective, and in cases with portal vein thrombosis in which other therapies are contra-indicated or ineffective.

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