**Title:**

**Reirradiation Stereotactic Body Radiotherapy for spine metastases from hepatocellular carcinoma: “Salvage the Bones”**

**Abstract**

Modern radiotherapy machines with refinements in planning software and image-guided apparatuses, have made Stereotactic body radiotherapy (SBRT) more widely available as an effective tool in the management of spine metastases. In conventional palliative radiotherapy the aim has traditionally been pain relief and short-term local control. In contrast, SBRT aims to deliver an ablative dose to enhance local control in a smaller number of fractions while sparing the organs at risk (OAR), especially the spinal cord. Recently, trials have asserted the role of spine SBRT as an effective modality for pain relief in addition to durable local control. The quality of evidence for spine SBRT data is maturing, while prospective published trials on re-irradiation SBRT in spine remains sparse. The purpose of the present case report is to share the challenges faced while salvaging a dorsal spine metastasis and ablating a new right adrenal metastatic lesion in close proximity of the transplanted Liver.

**Introduction**

Historically, linear accelerator was first used for spine SBRT in the year 1995 by Hamilton et al based on a rigid immobilization device (1). SBRT is defined as the precise irradiation of an image defined extra-cranial lesion associated with the use of high radiation dose delivered in a small number of fractions. Since its inception there has been tremendous progress in treatment delivery techniques ranging from Intensity modulate Radiotherapy (IMRT) to volumetric modulated arc therapy over the years, and modern day linacs deliver SBRT with sub millimetric accuracy. There have been dosimetric studies comparing Linac based systems to other radiosurgical systems like the cyberknife for intracranial lesions (2-Dutta et al). In addition, prospective clinical studies on spine SBRT for a range of spinal tumours have been published (3-Mahadev et al, 4-S Ryu RTOG 0631). Increasingly, centres across the globe have started doing SBRT on linear accelerators for spinal metastases. Recently, randomized trials have asserted the role of spine SBRT as effective modality not just for pain relief but durable local control as well in patients’ with oligometastases (5-SABR comet). The quality of evidence for spine SBRT data is maturing, while published data on re-irradiation SBRT in spine remains sparse. Systematic review articles have recommended reirradiation as an option for spinal metastases (6-Myrehaug et al). However, evidence is based on low-quality data. We herein report our experience with a patient who received reirradiation SBRT for spine metastases from a primary hepatocellular carcinoma (HCC), after his lesion progressed 15 months after SBRT.

**Case report**

A 69-year-old gentleman with Child A cryptogenic cirrhosis and a lesion involving the Right lobe of Liver was evaluated and diagnosed with a moderately differentiated hepatocellular carcinoma. Labs were done which revealed a non-B, non-C (NBNC; negative for hepatitis B antigen and hepatitis C antibody) and AFP non secreting multifocal hepatocellular carcinoma. Patient underwent living donor liver transplantation with a Right lobe graft in early September 2017. Post-surgery explant Liver histopathological examination confirmed a moderately differentiated hepatocellular carcinoma on a background of mixed nodular cirrhosis. Patient was doing well and was under regular follow up post-surgery. In August -2018 patient developed backache of one-week duration with significant limitation of activities daily living. MRI done showed a large lytic deposit in the D11 vertebra with pathological wedge compression, while the Epidural spinal cord compression grade was 1a with epidural impingement. PET-CT scan evaluation revealed a solitary lesion in the D11 spine suggestive of Oligometastatic-disease.

In a multidisciplinary tumour board comprising of a Spine surgeon, Neuroradiologist and radiation oncologist vertebral segment was scored based on the Spinal Instability Neoplastic Score (SINS) and was decided to go ahead with stabilization of the spine (7). Patient underwent D9-D11 percutaneous pedicle screw fixation and D11 biopsy, Biopsy was consistent with that of a metastatic hepatocellular carcinoma. Patient was given SBRT to the D11 spine with 24 Gy in 3 fractions using target (CTV) delineation guidelines proposed by the Radiosurgery consortium (8). Patient’s planning images with dose distribution and DVH-OAR data are shown in fig 1/ table 1. Patient experienced good pain relief post SBRT and was started on systemic therapy with Sorafenib.

In December-2019 patient complained of resurgence of pain in the back. Evaluation by MRI and PET CT imaging were done which revealed an osseous lysis with appearance of enhancing lytic soft tissue lesion involving the body of D11 vertebra. In addition to the vertebral lesion an enhancing FDG avid nodule in the Right Adrenal with enhancement was seen suggestive of disease progression. In our patient considering a gap of 15 months elapsed since last radiation and low volume oligometastatic disease it was decided in an MDT to offer reirradiation SBRT. Currently there are no validated models taking time interval between two courses of radiation into account. consequently, the time -dependent neurological function recovery largely remains speculative.

Proximity of the Right adrenal gland lesion, Right Kidney and the irradiated D11 spine to the transplanted Liver posed a challenge to deliver radiation safely to the target (D11 body and Right Adrenal gland). On account of the fact that it was a second course of radiation, target volume was limited to the body of the D11-vertebral body (Non donut shaped) to reduce toxicity. A dose of 30 Gy in 5 fractions was planned for the second course of SBRT. Reirradiation recommendations suggested by (9-Sahgal et al) were used as a guide to decide on dose limits to the critical neural tissues (CNT). For the remaining OAR we followed the AAPM\_TG-101 protocol as reference (10-Benedict et al). Dose to the transplanted Liver was kept as low as possible. Table1 / fig-2 show the technical characteristics of plans and dose parameters for both the SBRT courses. Patient completed reirradiation SBRT without any acute side effects and continues to remain pain free without any analgesics at 8 months follow up after treatment. In consideration of the fact that patient progressed on Sorafenib, he was started on Lenvatinib after the second course of SBRT.

How to talk about liver function being unaffected ? Labs /LFT –Normal ? / CT scan abdomen done mid of August 2020 shows stable disease. FINDINGS; Fig 3

**Discussion**

Extrahepatic metastases from HCC are estimated to be around 35 %, with Lung and the nodes being the commonest sites followed by bones (11-Katyal s et al 3. [doi.org/10.1148/radiology.216.3.r00se24698](https://doi.org/10.1148/radiology.216.3.r00se24698)). Although, the incidence of bone metastases in hepatocellular carcinoma is relatively low with studies estimating it to be 8 -18%, Isolated bone metastasis is not as uncommon as previously believed which in turn could be attributable to the better functional PET-CT imaging available widely over the last decade. Studies suggest that isolated bone metastasis patients have better outcomes while compared to those having metastases to other organs (12-Ho et al 10.1148/radiol.10100672).

The concept of oligometastatic state was proposed by Hellman and Weichsel Baum, which exemplifies an intermediary state of cancer between widely metastatic and curable, localized disease (13-[10.1200/JCO.1995.13.1.8](https://doi.org/10.1200/jco.1995.13.1.8)). Recently, a randomised, phase-2 clinical trial demonstrated a 13-month overall and a doubling of progression free survival benefit after SBRT in patients with controlled primary and one to five oligometastases (5-:<https://doi.org/10.1016/S0140-6736(18)32487-5>).

Prospective clinical studies on reirradiation SBRT spine are meagre, with only one phase I /II single institutional study (14-Garg et al). Predominantly, most of the published studies on spine Reirradiation SBRT are retrospective. However, outcomes in most of these studies were consistent with respect to diuturnal local control and pain relief (6-Myrehaug et al). Thibault et al in their retrospective report on salvage spine SBRT following in-field failure of initial SBRT for spinal metastases with a median time to failure of 11.7 months following first course of SBRT, concluded that salvage second course of spine SBRT is feasible and efficacious. In our patient time from the first SBRT course to local progression was 15 months, with a diffuse pattern of failure rather than the more common epidural disease progression. Possible explanation for this failure could be due to inherent tumour radioresistance. Adding on to the Gordian knot, patient was a post living donor liver transplant survivor who experienced progression with interval appearance of a new right adrenal lesion and progression in the D11 spine. Proximity of the Right Adrenal gland lesion and the irradiated D11 spine to the transplanted Liver posed a challenge to deliver radiation safely to the complex target volume while avoiding critical organs at risk (transplanted Liver & cord).

In addition to having limited metastatic burden our patient was an AFP non secretor. Non secretion of AFP at diagnosis has shown to be an important determinant for overall survival in post-transplant patients in a study utilizing the scientific registry of transplant recipients database and in locally advanced HCC patients treated with Sorafenib in a retrospective study (15-Toso et al, 16-Afshar et al). An improved outcome due to better clinical care and favourable disease characteristics eventually leads to more number of patients presenting with vertebral metastases. Furthermore, long term survivors will experience not just pain but also local tumour progression and consequently need reirradiation to salvage the bones.

Recently, a single institution retrospective study reported that proton-ablative radiation therapy to primary HCC was associated with better survival, probably due to decreased incidence of posttreatment Liver decompensation (17-Sanford et al.). They hypothesize that Bragg peak phenomenon a distinctive feature of proton therapy reduces the low dose bath distal to the target beam path associated with photons. The figure-x shows how we placed Four partial arcs with avoidance sector to reduce low dose bath to the transplanted liver for both the spine SBRT courses. To our knowledge this is the first published case report on reirradiation SBRT to spine in a living donor liver transplant patient from the Indian subcontinent.

**Conclusion:** The present case report suggests that reirradiation spine SBRT is feasible and may be a reasonable option if used judiciously in a select group of patients wherein one is able to deliver an adequate dose to the target while respecting the CNT tolerance. Moreover, with ever increasing armamentarium of effective systemic therapies, local control of limited metastatic sites has a potential to positively influence long term clinical outcomes.

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|  | **SBRT**  **(1st - Course)** | **Reirradiation-SBRT**  **(2nd - Course)** |
| **Target Parameters** |  |  |
| **CTV**  Shape  Volume (cc) | Donut  103.8 | Non-Donut  52.5 |
| **PTV**  Volume (cc) | 152.3 cc | 75 cc |
| **Planning Technique**  **No. of arcs**  **Arc Geometry**  **Avoidance sector**  **Dose fractionation**  **D1%**  **D95 %**  **Conformity Index** **CI)**  Volume of prescription Isodose/ Volume of PTV  **Homogeneity index (HI)**  (D2 / D98)  **Gradient Index**  (PTV/V50) | VMAT  4  Partial  20°-210°  24 Gy in 3 Fractions  95%  1.09  1.16  2.44 | VMAT  4  Partial  20°-210°  30 Gy in 5 Fractions  95%  1.23  1.13  3.89 |
| **Organs at Risk OAR** |  |  |
| **Cord**  <0.35 cc  < 1.2 cc | 24.6  24.2 | 13  11.2 |
| **Critical Neural Tissue\_nBED** | 48 Gy (nBED-From 1st SBRT) | True cord dose was kept <16 Gy in 5 fraction regimen |
| **Transplanted-Liver**  **Volume**  **D1cc**  **V5**  **V21** | 1230 cc  -----  350.6 cc  - | -----  181.7 cc  7.3 cc |
| **Esophagus D1cc**  **Stomach**  **Dmax**  **16 Gy< 10 cc** | 16.6 Gy  11 Gy<10cc | 18.2 Gy  16 Gy <7cc |
| **Right Kidney**  **Volume**  Dmax  >200 cc  **Dmean** | 216.9 cc |  |
| **Beam Energy** | 10 MV-FFF | 10 MV-FFF |
| **Total MU(Monitor Units)** | 2297 | 2205 |