



Re-irradiation after stereotactic body radiotherapy for spine metastases from hepatocellular carcinoma: a case report

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ABSTRACT

Modern radiotherapy machines with refinements in planning software and image-guidance 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, with 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 durable local control, in addition to achieving pain relief. The quality of evidence for spine SBRT data is maturing, while prospective published trials on re-irradiation SBRT in spine remain 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 proximity of the transplanted liver.

Key words: SBRT; re-irradiation; hepatocellular carcinoma; oligometastases; spine metastases

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Introduction

Historically, a linear accelerator (linac) was first used for spine stereotactic body radiotherapy (SBRT) in the year 1995 by Hamilton et al. based on a rigid immobilization device [1]. SBRT is defined as 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 over the years, ranging from Intensity Modulated Radiotherapy (IMRT) to Volumetric Modulated Arc Therapy (VMAT), 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]. In addition, case reports, prospective clinical studies and review articles on liver and spine SBRT for a range of tumours have been published [3–6]. Increasingly, centres across the globe are utilizing linac based SBRT for spinal metastases.

Recently, a large single institution series and a randomized trial postulated the role of spine SBRT as an effective modality not just for pain relief but local control as well in patients with oligometastases [7, 8]. The final results from phase 3 randomized trials albeit would give insights into the actual benefits in terms of outcomes. The qual-

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ity of evidence for spine SBRT data is maturing, while published data on re-irradiation after SBRT in spine remains exiguous. A recent systematic review article has recommended re-irradiation as an option for spinal metastases [9]. However, evidence is based on low-quality data. We herein report our experience with a patient who received re-SBRT for dorsal (D) spine metastases from a primary hepatocellular carcinoma (HCC), after his lesion progressed 15 months after first SBRT.

Case presentation

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. Laboratory investigations revealed a non-B, non-C (NBNC; negative for hepatitis B antigen and hepatitis C antibody) and a non-alpha fetoprotein (AFP) secreting multifocal HCC. Post-surgical explant liver was of 25 × 17 × 10 cm size and the cut surface of the right lobe revealed a lesion measuring 6 × 6.5 cm. Histopathology disclosed a diagnosis of moderately differentiated HCC (Edmondson and Steiner grade 3). Microvascular invasion was present. Perineural invasion was not identified. The hilar vascular and duct margins were free of tumour. There was no tumour invasion identified in the major branches of portal and hepatic veins. Patient was doing well and was under regular follow up post-surgery. In August 2018, the patient developed back pain of one-week duration with significant limitation of activities of daily living. MRI showed a large lytic deposit in the D11 vertebra with wedge compression, while the Epidural spinal cord compression was Bilsky grade 1a with epidural impingement. Fluoro-2-deoxy-D-glucose (FDG) PET-CT scan revealed a solitary lesion in the D11 spine, suggestive of oligometastatic disease.

In a multidisciplinary tumour board (MDT) comprising a Spine surgeon, Neuroradiologist and Radiation Oncologist, vertebral segment was scored based on the Spinal Instability Neoplastic Score (SINS), and was decided to proceed with surgical stabilization of the spine [10]. Patient underwent D9-L1 percutaneous pedicle screw fixation and D11 biopsy. Histopathological examination was consistent with that of a metastatic HCC. Two weeks post surgery the patient received SBRT to the

D11 spine with a dose of 24 Gy in 3 fractions using target delineation guidelines proposed by the radio-surgery consortium [11]. VMAT based plans were optimized in the Eclipse treatment planning system (TPS) using 10 MV (Flattening filter free beams) for multiple arcs of varying length for a Truebeam STx (Varian Medical Systems, USA) equipped with high definition multileaf collimator (HDMLC) with 120 leaves. Patient's planning images with dose distribution is shown in Figure 1. Patient experienced good pain relief post SBRT and was started on systemic therapy with Sorafenib.

In December 2019 the patient complained of resurgence of pain in the back. Evaluation with MRI and FDG PET-CT imaging were done to reveal 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 was seen in the right adrenal with enhancement, suggestive of disease progression. In our patient, considering a gap of 15 months since last radiation and low volume oligometastatic disease, it was decided in MDT to offer re-irradiation with SBRT. Currently, there are no validated models taking into account time interval between two courses of radiation. 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 in delivering 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. Re-irradiation recommendations suggested by Sahgal et al. [12] were used as a guide to decide on dose limits to the critical neural tissues (CNT). For the remaining OARs, we followed the report of the American Association of Physicists in Medicine Task Group-101 as reference [13]. Dose to the transplanted liver was kept as low as possible. Table 1 shows the technical characteristics of plans and dose parameters for both SBRT courses. Patient completed re-irradiation SBRT without any acute side effects and continues to remain pain free without any analgesics at 8 months follow up after treatment. In view of the fact that patient progressed on

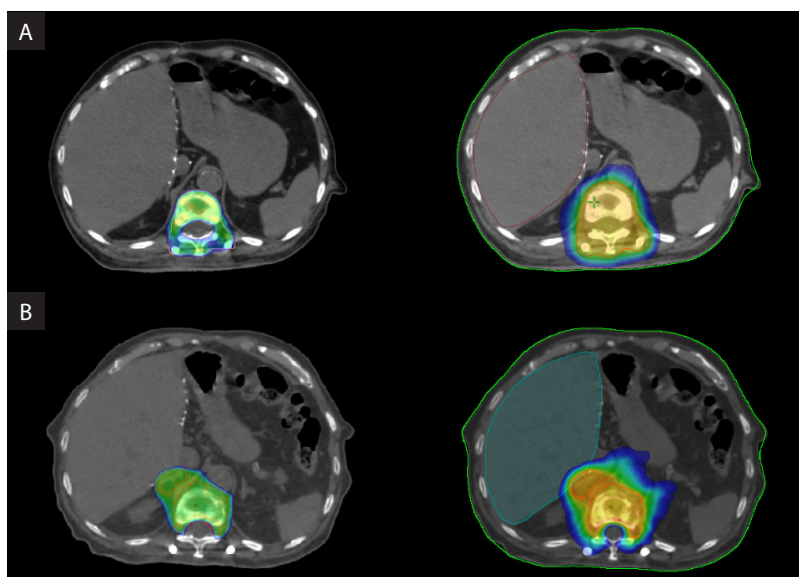


Figure 1. Patient's planning images with dose distribution. Dose in colour wash showing 85% and 50% isodose. **A.** First course of spine stereotactic body radiotherapy (SBRT) (24 Gy in 3 Fractions); **B.** Re-SBRT spine (30 Gy in 5 fractions)

Table 1. Technical characteristics of plans and dose parameters for both the stereotactic body radiotherapy (SBRT) courses

Parameters	SBRT (1 st course)	Re-irradiation SBRT (2 nd course)	Cumulative dose
PTV			
Shape	Donut	Non-Donut	
Volume [cm ³]	152.3	75.0	
Dose fractionation	24 Gy in 3 fractions	30 Gy in 5 fractions	
PTV coverage (D _{95%})	95%	95%	
Conformity Index (CI)	1.09	1.18	
Homogeneity Index (HI)	1.16	1.13	
Gradient Index (GI)	2.44	3.29	
Organs at risk (OARs)			
Spinal cord			
D _{0.35cm³} EQD2 [Gy]	35.0	15.1	50.1
D _{1.2cm³} EQD2 [Gy]	32.9	11.9	44.8
D _{max} EQD2 [Gy]	40.3	20.8	61.1
Transplanted liver			
V _{5Gy} [cm ³]	350.6	181.7	
V _{21Gy} [cm ³]	0.0	7.3	
Stomach			
D _{max} EQD2 [Gy]	21.0	23.8	44.8
Duodenum			
D _{max} EQD2 [Gy]	4.4	0.3	4.7
Bowel			
D _{max} EQD2 [Gy]	5.6	15.1	20.7
Right kidney			
V _{16Gy} [cm ³]	0.0	1.8	

PTV — planning target volume; Gy — Gray; cm³ — cubic centimetre; D_{x cm³} — dose received by x cm³ of volume; V_{xGy} — volume receiving x Gy dose; D_{max} — maximum dose; EQD2 — equivalent dose in 2 Gy

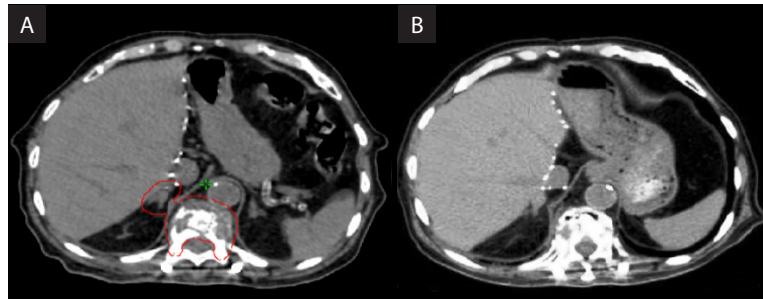


Figure 2. A. Re-SBRT spine planning image; B. Recent follow-up image showing stable disease

Sorafenib, he was started on Lenvatinib after the second course of SBRT. Most recent assessment in August 2020 showed liver function within normal limits, and CT abdomen showing stable disease (Fig. 2).

Discussion

Extrahepatic metastases from HCC are estimated to be around 35%, with lung and lymph node being the most common sites followed by bones [14]. Although, the incidence of bone metastases in HCC is relatively low with studies estimating it to be 8-23%, isolated bone metastasis is not as uncommon as previously believed, which could be attributed to increased utilization of higher sensitivity radiography for staging, particularly utilization of FDG PET-CT. Studies suggest that patients with isolated bony metastatic disease have improved outcomes in comparison to those with visceral organ metastases [15].

The concept of oligometastatic state was proposed by Hellman and Weichselbaum, [16] which exemplifies an intermediary state of cancer between widely metastatic and curable, localized disease. 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 [8].

Prospective clinical studies on re-irradiation after SBRT spine are meagre, with only one phase I/II single institutional study [17]. Predominantly, most of the published studies on spine re-irradiation after SBRT are retrospective. Nevertheless, outcomes in most of these studies were consistent with respect to sustained local control and pain relief [9]. Thibault et al. [18], in their retrospec-

tive 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. This failure could possibly be explained by inherent tumour radioresistance. Adding on to the complexity, patient was a post 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 in delivering radiation safely to the complex target volume while avoiding critical organs (transplanted liver and spinal 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 [19, 20]. An improved outcome due to better clinical care and favourable disease characteristics eventually leads to a greater number of patients presenting with vertebral metastases. Furthermore, long term survivors will experience not just pain but also local tumour progression and, consequently, might need re-irradiation.

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 post-treat-

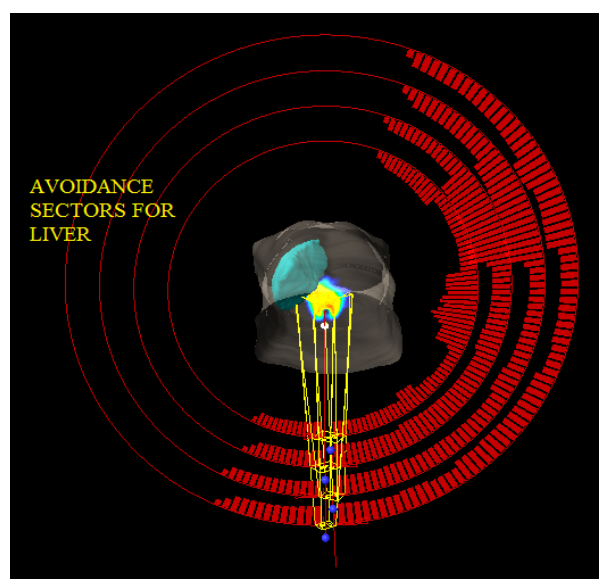


Figure 3. VMAT arc arrangement — four partial arcs with avoidance sector

ment liver decompensation [21]. Authors 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 3 shows how we placed four partial arcs with avoidance sector to reduce low dose bath to the transplanted liver for both spine SBRT courses. To our knowledge, this is the first published case report on re-irradiation after SBRT to the spine in a living donor liver transplant recipient from the Indian subcontinent.

Conclusion

The present case report suggests that re-irradiation after 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 critical neural tissue tolerance. Moreover, with ever increasing armamentarium of effective systemic therapies, local control of limited metastatic sites has a potential to positively influence the long term clinical outcomes.

Conflict of interest

The authors declare no conflicts of interest.

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