Stereotactic Body Radiotherapy for Osseous Low Alpha-Beta Resistant Metastases for Pain Relief - SOLAR-P

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Background

The use of stereotactic body radiotherapy (SBRT) has been a topic of interest in palliative approaches for managing metastatic disease. Advances in radiation planning and delivery allows clinicians to target lesions with higher, ablative doses to tumors, while minimizing dose to organs and tissues at risk. SBRT has been demonstrated to be effective in controlling local metastatic lesions, while delaying distant progression of disease within the context of several retrospective, and small prospective randomized trials (1,2).

The use of SBRT is appealing, in particular, for tumors with low alpha-beta ratios such as prostate cancer, breast cancer, renal cell carcinoma (RCC), melanoma, and sarcoma. Such tumors have inherent radioresistance to standard fractionation regimens, and benefit from dose escalation in order to yield more potent biological efficacy. Theoretically, this may lead to amplification of vascular damage, increased endothelial cell apoptosis, and enhanced antitumor immunity (3). Low alpha-beta tumors classically respond to higher doses per fraction, as demonstrated in pre-clinical studies for instance using renal cell cancer cell lines (4), and in clinical studies suggesting equivalent or improved local control using more hypofractionated radiation regimens (5,6). The higher doses in fewer fractions theoretically may overcome innate tumor radioresistance resulting in improved local control and symptom resolution.

Palliative radiotherapy (RT) has been common practice in managing painful bone metastases, and classically this has been administered in conventional fractionation schedules such as 20 Gray (Gy) in 5 fractions or 8 Gy in a single fraction. RT has been established an effective, low-risk approach for uncomplicated symptomatic bone metastases, and a meta-analysis showed overall response rate of 60% and complete response rate of 23-24% (7). Following RT, median time to onset of pain relief was 1-4 weeks, and median duration of response was 3-6 months. Multiple studies have shown no significant differences in outcomes between single fraction and multiple fraction regimens, though following single fraction there was a higher chance of retreatment (8-11).

Retreatment with palliative RT has also been shown to be effective following no response or symptomatic relapse after initial treatment. In the per-protocol analysis, the SC20 trial reported that patients retreated with 8 Gy/1 fraction and 20 Gy/5 fractions had pain response rates of 45% and 51%, respectively at 2 months post-treatment (12). Overall, 48% of patients who received their assigned treatment had reduced pain at the site of repeat radiation, regardless of whether or not they responded to their initial treatment. In addition, 68% had improved quality of life pain scores.

SBRT has shown promising early results in the management of bone metastases. In addition to its utility in spinal lesions, SBRT has been reported to improve local control in prostate cancer bone metastases with reductions of in-field failure in comparison to hypofractionated schedules (13), but it was unclear whether this translated into long term pain relief. Also, there has been some research in the use of SBRT in RCC bone metastases, given its resistance to conventional fractionation. One study showed that SBRT improved symptom control rates at 10, 12 and 24 months in comparison to standard external beam RT, with a median time to control of 2 weeks (14), but documentation of pain control was variably captured, and largely extrapolated from clinical notes. Other retrospective data in RCC, melanoma and sarcoma suggested a high degree of pain relief in patients treated with SBRT for spine metastases, however pain scores were not prospectively captured (15), and the study was likely to be underpowered to determine a significant effect. In addition, a recent phase II randomized trial that included patients with bone metastases from all disease sites (majority lung), showed that single fraction SBRT had higher rates of pain response at 2 weeks and 3 months compared to conventional fractionation (16). However, the degree of pain response in the control group was less than expected, the majority of the patients on this study did not have low alpha-beta tumors, and the radiation dose schedule in the conventional arm was not typical of standard practice (30 Gy in 10 fractions as compared to 8 Gy/1 fraction or 20 Gy/ 5 fractions).

Currently, there is a paucity of prospective data studying the use of SBRT for bone metastases originating from low alpha-beta tumors, with systematic reporting of changes in pain scores and analgesia use over time. The vast majority data looking at SBRT in bone lesions focuses on local control and survival, rather than more tangible outcomes in a palliative population including symptomatic control, durability of response (and need for retreatment), and patient reported quality of life; a component that is understudied in this group despite its tremendous value. Furthermore, SBRT for bone metastases has yet to become common practice given the limited evidence for its efficacy and uncertainty in regards to toxicity.

We propose an investigation of the potential benefits of SBRT for symptomatic bone metastases in patients with prostate cancer, breast cancer, RCC, melanoma, and sarcoma. We look to conduct a prospective cohort study (SOLAR-P) that is adequately powered to analyse efficacy in alleviating pain from bone lesions and compare this to well-established rates in literature for conventionally fractionated palliative RT. We will also assess the tolerability of this modality, toxicity rates, and effect on quality of life. If our results show that SBRT has a significant benefit on this population, the goal would be to pursue a larger randomized trial to confirm the findings.

Methods

Patient Population:

Patients will be accrued from the Juravinski Cancer Centre. Eligibility will be determined based on the criteria listed below, and informed consent will be established.

- Inclusion
    - Diagnosis of prostate cancer, breast cancer, renal cell carcinoma, or melanoma
    - Radiographic evidence of bone metastases requiring treatment for pain
    - BPI score of ≥ 2
- Exclusion
    - Spinal lesions
    - Severe or progressive neurological deficit
    - Impending (Mirels' score ≥9) or existing pathological fracture
    - Bone metastasis in a previously irradiated site
    - Active concurrent systemic therapy
    - > 5 lesions requiring treatment
    - Lesions > 5 cm in largest diameter
    - Life expectancy < 3 months
    - Age < 18
    - KPS < 50
    - Unable to provide informed consent

Primary Outcome:

- **Overall Pain Response at 3 months**: Assessed using the Brief Pain Inventory (BPI; Appendix A) and converting daily analgesic use to oral morphine equivalent (OME)
    - *Complete response* defined as BPI pain score of 0 with no increase in OME.
    - *Partial response* defined as BPI pain score of >0, and either a reduction of 2 or more with no increase in OME, or no increase in BPI with a reduction in OME or at least 25%.
    - *Treatment failure* defined as worsening pain on BPI by 2 or more, >50% increase in OME, re-irradiation for pain/progression, or development of pathologic fracture.

Secondary Outcomes:

- **Overall Pain Response at 1 month and 6 months post SBRT:** Assessed using the BPI and response as described above.
- **Toxicity:** Acute (3 months or less), and late (greater than 3 months) adverse effects from RT will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 (17).
- **Patient-reported QoL:** QoL assessed by European Organization of Research and Treatment of Cancer Quality of Life -Questionnaire-Core-15-Palliative (EORTC QLQ-C15-PAL) and EORTC QLQ-Bone Metastasis 22 (EORTC QLQ-BM22), measured at 1, 3, and 6 months post SBRT (18,19).
- **Rate of Re-irradiation and Salvage Surgery due to symptomatic progression:** Patients requiring re-irradiation will not undergo treatment for at least 4 weeks following the study radiation course. Patients requiring salvage surgery for disease progression, instability, or pathologic fractures will be reported.

- **Local Control of Treated Lesions:** To be assessed retrospectively using standard of care follow-up imaging. Radiographic control evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (20).

Intervention and Evaluation

Pre-Treatment Evaluation:

Patient eligibility will be determined during the initial assessment which includes a physical examination and review of radiographic evidence of metastases. Fracture risk will be assessed based on Mirels' Staging System taking into account the clinical evaluation and imaging available. For patients with high clinical suspicion of impending fracture, further evaluation may be taken with plain film radiographs as per standard of care.

An initial BPI will be completed prior to treatment during a clinic visit, or over the phone. Use of analgesic medications will be recorded.

Treatment Plan:

Enrolled patients will receive the study dose of 15 to 20 Gy in 1 fraction to all painful bony lesions with SBRT. Planning and delivery will be conducted using a volumetric modulated arc therapy (VMAT) approach on our Varian Truebeam platform. Patients will be CT simulated, with a vac-lock immobilization. Use of 4DCT will be dependent on the area being treated. The gross tumor volume (GTV) will be defined as the visible abnormality based on CT imaging. The planning target volume (PTV) will be an additional 5 mm in all directions. The SBRT prescription will ensure that at least 95% of the PTV will be covered with the prescribed dose, and that at least 99% of the PTV will be covered by 95% of the prescription dose. Dose to organs at risk will based on institutional guidelines for single fraction SBRT. Daily image guidance will be performed using cone beam CT aligning to relevant bony anatomy +/- PTV if visible.

Evaluation During Study:

The primary outcome will be overall pain response, measured using the BPI. Patients will be assessed using the BPI at baseline, and then at 1 month, 3 months, and 6 months following the completion of the SBRT treatment course. Responses will be obtained by patient self-reported questionnaires in clinic or by telephone follow-up. The sum of responses will dictate the overall response to treatment. Patients will be seen once for treatment review during their SBRT course to document acute toxicity. They will also be assessed at the 1 month, 3 month, and 6 month intervals to record acute and late toxicity using CTCAE version 5.0. Quality of life will be measured using the EORTC QLQ-C15-PAL and BM22 questionnaires at the same timepoints.

Sample Size and Statistical Analysis

Sample size:

The estimated pain response at 3 months using cRT is approximately 60% (null hypothesis is that SBRT will have a response of 60% as well). However, we postulate that the pain response at 3 months using SBRT will be 80% (alternative hypothesis). Given 80% power, two-sided alpha of 0.05, we will require 41 patients to test this hypothesis using a one sample binomial test. We plan to recruit 45 patients to account for any losses to follow-up.

Statistical Analysis:

The observed proportion of pain response at 3 months with SBRT will be compared to the null value of 0.6 using a one sample binomial test. The corresponding 95% confidence interval (CI) around the observed proportion will be calculated using the Wilson score method.

Study Timeline

0-12 Months: Patient accrual, consent, RT planning and delivery.

12-18 Months: Ongoing follow-up of study patients, planned assessments at designated intervals for pain, toxicity and quality of life parameters.

18-24 Months: Data analysis, reporting and publication phase.

Appendix A. Brief Pain Inventory

1903

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

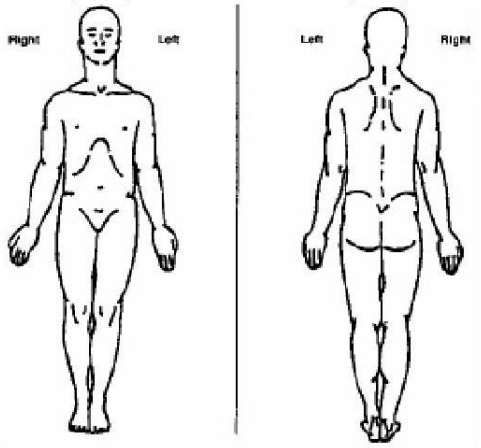
Revision: 07/01/05

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

1. Palma D, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;393:2051—58.

2. Gomez D, Blumenschein G, Lee J, et al. Local Consolidative Therapy versus Maintenance Therapy/Observation for Patients with Oligometastatic Non-Small Cell Lung Cancer without Progression after Front-Line Systemic Therapy: Results of a Multi-Institutional Phase II Randomized Study. Lancet Oncol 2016;17:1672—82.

3. Brown J, Carlson D, Brenner D. The Tumor Radiobiology of SRS and SBRT: Are More than the 5 R's Involved? Int J Radiat Oncol Biol Phys 2014;88:254—62.

4. Ning S, Trisler K, Wessels B, et al. Radiobiologic studies of radioimmunotherapy and external beam radiotherapy in vitro and in vivo in human renal cell carcinoma xenografts. Cancer 1997;80:2519—28.

5. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394:385—95.

6. Zaorsky N, Lehrer E, Kothari G, et al. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. Eur Urol Oncol 2019;S2588-9311:30074-4.

7. Chow E, Zeng, L, Salvo, N, et al. Update on the Systematic Reivew of Palliative Radiotherapy Trials for Bone. Clinical Oncology 2011;24:112—24.

8. Amouzegar-Hashemi F, Behrouzi H, Kazemian A, et al. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. Curr Oncol 2008;15:151.

9. Hamouda WE, Roshdy W, Teema M. Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. Gulf J Oncol 2007;1:35—41.

10. El-Shenshawy H, Kandeel A, El-Essawy S. The effect of a single fraction compared tomultiple fractions radiotherapy on painful bone metastases with evaluation of computed tomography bone density in osteolytic bone metastases. Bull Alex Fac Med 2006;42:439.

11. Foro Arnalot P, Fontanals AV, Galceran JC, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiother Oncol 2008;89:150—155.

12. Chow E, Linden Y, Roos D, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol 2014;15:164—71.

13. Gao R, Olivier K, Park S, et al. Stereotactic Body Versus Hypofractionated Radiation Therapy for Local Control of Prostate Cancer Bone Metastases. Int J Radiat Oncol Biol Phys 2018;102:S108.

14. Amini A, Altoos B, Bourlon M, et al. Local control rates of metastatic renal cell carcinoma to the bone using stereotactic body radiation therapy: Is RCC truly radioresistant? Pract Radiat Oncol 2015;5:589—96.

15. McGee H, Carpenter T, Ozbek U, et al. Analysis of Local Control and Pain Control After Spine Stereotactic Radiosurgery Reveals Inferior Outcomes for Hepatocellular Carcinoma Compared With Other Radioresistant Histologies. Pract Radiat Oncol 2019;9:89—97.

16. Nguyen Q, Chun S, Chow E, et al. Single-Fraction Stereotactic vs Conventional Multifraction Radiotherapy for Pain Relief in Patients With Predominantly Nonspine Bone Metastases A Randomized Phase 2 Trial. JAMA Oncol 2019;5:872—8.

17. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. National Cancer Institute, Division of Cancer Treatment & Diagnosis. 2017. Published online: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5.0.xlsx.

18. Groenvold M, Petersen M, Aaronson N, et al. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. Eur J Cancer 2006;42:55—64.

19. Chow E, Hird A, Velikova G, et al. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for patients with bone metastasis: the EORTC QLQ-BM22. Eur J Cancer 2009; 45:1146-52.

20. Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228—47.