e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2023, Volume 28, Number 3, pages: 379–388
DOI: 10.5603/RPOR.a2023.0037
Submitted: 29.11.2022
Accepted: 05.06.2023

Spine Patient Optimal Radiosurgery Treatment for Symptomatic Metastatic Neoplasms (SPORTSMEN): a randomized phase II study protocol

Shearwood McClelland III[1, 2], Yilun Sun[1], Daniel E. Spratt[1]

[1]Department of Radiation Oncology, University Hospitals Seidman Cancer Center Case Western Reserve University School of Medicine, Cleveland, OH, United States
[2]Department of Neurological Surgery, University Hospitals Seidman Cancer Center Case Western Reserve University School of Medicine, Cleveland, OH, United States

ABSTRACT

Background: Approximately 40% of patients with metastatic cancer will have spinal metastatic disease. Historically treated with external beam radiation therapy (EBRT) with limited durability in pain control, the increased lifespan of this patient population has necessitated more durable treatment results via spine radiosurgery/stereotactic body radiation therapy (SBRT). The goal of this study is to assess three-month pain freedom rates via the Spine Patient Optimal Radiosurgery Treatment for Symptomatic Metastatic Neoplasms (SPORTSMEN) randomized trial.

Materials and methods: This study is a prospective randomized three-arm phase II trial which will recruit patients with symptomatic spine metastases. All patients will be randomized to standard-of care SBRT (24 Gy in 2 fractions), single-fraction SBRT (19 Gy in 1 fraction), or EBRT (8 Gy in 1 fraction), with the primary endpoint of three-month pain freedom (using the Brief Pain Inventory). We expect that SPORTSMEN will help definitively answer the efficacy of spine SBRT versus EBRT for achieving pain freedom, while defining the safety and efficacy of 19 Gy single-fraction spine SBRT. Local control will be defined according to Spine Response Assessment in Neuro-Oncology (SPINO) criteria.

Discussion: This is the first phase II trial to objectively assess optimal spine SBRT dosing in the treatment of symptomatic spine metastatic disease, while assessing spine SBRT versus EBRT. Findings should allow for better determination of the efficacy of two-fraction spine SBRT versus EBRT in the United States, as well as for the novel single-fraction 19 Gy spine SBRT regimen in patients with symptomatic spine metastases.

Trial Registration: Clinicaltrials.gov identifier: NCT05617716 (registration date: November 14, 2022).

Key words: spine radiosurgery; stereotactic body radiation therapy; external beam radiation therapy; spine metastases; pain freedom

Rep Pract Oncol Radiother 2023;28(3):379–388

Address for correspondence: Shearwood McClelland III, MD, Department of Radiation Oncology, University Hospitals Seidman Cancer Center, 11100 Euclid Avenue, Lerner Tower Office Suite B161, Cleveland, OH 44106, United States, tel: 216-286-4149; e-mail: drwood@post.harvard.edu

Introduction

Metastatic spine cancer incidence is increasing; the primary treatment is radiation therapy. Approximately 40% of all patients with metastatic cancer have spine metastatic disease, with nearly 200,000 new cases of spine metastases occurring annually in the United States [1–3]. Metastatic spine disease has been historically treated with external beam radiation therapy (EBRT) with conventional fractionation over 1–2 weeks, with relatively limited durability in pain control [4]. The increased lifespan of patients with metastatic cancer has resulted in an increase in the incidence of spine metastases, which has led to a need for more durable treatment results. To this end, stereotactic radiosurgery (SRS)/stereotactic body radiation therapy (SBRT) of the spine has exponentially increased in popularity since first being reported in 1995 [5–7], with the theoretical advantages of higher tumoricidal dose and more rapid fall off between tumor and surrounding normal tissue compared with EBRT.

Clinical data to date

The result of a single randomized trial has revealed that SBRT provides superior, more durable pain control of metastatic spine cancer than EBRT. The results of this recent Phase II/III randomized trial (CCTG SC.24/TROG 17.06) involving 229 patients over a five year period revealed that for patients with symptomatic metastatic spine disease involving no more than three contiguous levels, spine SBRT of 24 Gray (Gy) in 2 fractions compared to external beam radiation therapy (20 Gy in 5 fractions) provided superior freedom from pain (using the Brief Pain Inventory) at three-months post treatment (35% *vs*. 14%; $p < 0.001$) which remained durable at six-months post-treatment (32% versus 16%; $p = 0.004$) [8, 9]. However, this trial did not involve any patients from the United States, where the question of the superiority of SBRT over EBRT remains to the point where insurance companies may deny coverage of SBRT over EBRT in this patient population.

Rationale

Disparities exist in utilization of spine SBRT. Despite the superiority of SBRT over EBRT in the treatment of metastatic spine cancer from the SC.24 trial, disparities in spine SBRT utilization exist and have unfortunately remained prevalent. Previous nationwide analyses conducted over a 10-year period indicate that race and insurance status are independently associated with reduced receipt of SBRT [4, 7].

Specifically, African-American race has been associated with 20% reduced likelihood of receiving spine SBRT and Medicaid insurance associated with 30% reduced likelihood of receiving spine SBRT [4]. These findings are unfortunately consistent with an overarching trend in oncology involving racial disparities in receipt of optimal radiation therapy regardless of disease site [10–15].

The optimal SBRT treatment regimen for metastatic spine cancer has yet to be established. While the 24 Gy in 2 fraction radiosurgery course has been well-characterized in both the aforementioned randomized trial and in a single-center retrospective study [8, 16], it is unclear whether this regimen is in fact optimal for providing pain freedom in metastatic spinal disease. While there has been variable data for 1, 2, 3, and 5 fraction spine SBRT — each of which have been used for several years [7], there have been no randomized controlled trials to date specifically comparing spine SBRT dosing regimens.

Consequently, we propose the Spine Patient Optimal Radiosurgery Treatment for Symptomatic MEtastatic Neoplasms (SPORTSMEN) multicenter randomized Phase II clinical trial. The SPORTSMEN trial proposes to determine the optimal spine radiosurgery/SBRT dose, comparing 24 Gy in 2 fractions to 19 Gy in 1 fraction in the SBRT arms. With comparable biologically effective doses and biologically equivalent doses (Tab. 1), this trial will be the first to provide ob-

Table 1. Dose equivalent measurements of the Spine Patient Optimal Radiosurgery Treatment for Symptomatic Metastatic Neoplasms (SPORTSMEN) spine stereotactic body radiation therapy (SBRT) treatment arms

Spine SBRT regimen	24 Gy in 2 fractions	19 Gy in 1 fraction
BED	52.8 Gy	55.1 Gy
EQD2	44.0 Gy	45.92 Gy
α/β ratio	10 Gy	10 Gy

BED — biologically equivalent dose; EQD2 — equivalent total dose in 2-Gy fractions

jective data in assessing optimal spine SBRT dosing. A novel concept, the SPORTSMEN trial has the potential to reduce spine SBRT treatment to a single fraction which could markedly reduce financial toxicity and racial disparities in treatment completion in a manner similar to the potential for the recently adopted ultrahypofractionated FAST-Forward radiation treatment regimen for breast cancer [17, 18]. As the superiority of SBRT over EBRT has yet to be established in the United Sttes, the third arm of this trial involves conventional EBRT (8 Gy in 1 fraction).

The 19 Gy in 1 fraction arm was arrived upon based on the following evidence:

- A — shorter time of treatment for the patient compared with multiple fractions [19];
- B — higher dose than that tested in a previous prospective (and to-date unpublished) RTOG 0631 trial comparing single-fraction SBRT versus EBRT where only 45% of patients received 18 Gy x 1 and 55% of patients received 16 Gy x 1 (this trial used a pain scale criteria which unlike the Brief Pain Inventory did not account for mechanical instability components of spinal pain) and retrospective work assessing failure-free survival [20];
- C — a nationwide analysis revealed single-fraction to be the most popular spine SBRT fractionation scheme in the United States [7];
- D — recent work examining post-SBRT vertebral compression fracture (VCF) revealed that minimizing VCF risk occurs when the percentage of the vertebral body receiving at least 20 Gy is less than 24% for single-fraction SBRT, which is consistent with earlier work demonstrating significantly increased risk of VCF for spine SBRT of 20 Gy/fraction or greater [21, 22] including an unacceptably high VCF rate of 39% previously demonstrated for 24 Gy single-fraction spine SBRT [23];
- E — The 19 Gy x 1 will provide the highest biologically equivalent dose (BED) and equivalent total dose in 2-Gy fractions (EQD2) of any treatment arm (Tab. 1), yet remaining low enough to consistently meet the spinal cord maximum dose (Dmax) constraint of 14 Gy and cauda equina Dmax constraint of 16 Gy for single-fraction spine SBRT (Tab. 2) [24].

Given the frequency of spine involvement in metastatic cancer, the implications of SPORTSMEN are far-reaching as a prospectively determined optimal spine SBRT dose will impact a large number of medical subspecialties in addition to radiation oncology. The short and long-term results of the recent Phase II SABR-COMET randomized trial demonstrating improved durable overall survival for oligometastatic disease treated with SBRT versus palliative standard-of-care only further illustrate the increasing importance of SBRT for metastatic spine disease and, therefore, the necessity of determining the optimal spine SBRT treatment regimen [25, 26]. Treatment arms would be stratified by the following disease demographics: 1 — Intermediate versus radioresistant histology; 2 — presence/absence of epidural disease (for which the Bilsky scale for epidural spinal cord compression will be used [27]); 3 — Baseline opiate use; 4 — Baseline pain score; 5 — Extent of disease; 6 — Remaining lines of standard of care therapy available (0–1 *vs.* 2+).

Table 2. Critical structures

	Maximum point dose constraint	D0.1cc constraint
Organ at risk	24 Gy in 2 fractions	19 Gy in 1 fraction
Spinal cord (no PRV)		14 Gy
Spinal cord + 0.2 cm PRV	17 Gy	16 Gy
Cauda equina (no PRV)	17 Gy	16 Gy
Esophagus	20 Gy	16 Gy
Trachea	20 Gy	20 Gy
Pharynx	20 Gy	N/A
Stomach	20 Gy	14 Gy
Rectum	20 Gy	18 Gy
Duodenum		16 Gy
Small bowel	20 Gy	11 Gy
Large bowel (colon)	20 Gy	16 Gy
Kidneys	26 Gy	N/A
Liver	26 Gy	N/A
Sacral nerve roots (to be contoured for tumors involving S1–S5)	26 Gy	18 Gy
Heart		22 Gy
Great vessels		18 Gy
Brachial plexus		17.5 Gy
Brainstem		14 Gy

PRV — planning risk volume; N/A

Materials and methods

Objective(s)

Primary objective was to evaluate pain freedom from symptomatic metastatic spinal disease at 3 months following treatment (two-fraction standard-of-care spine SBRT, one-fraction spine SBRT, or EBRT), defined using the Brief Pain Inventory for assessment [9].

Secondary objectives were:

- 6-month freedom from pain, defined as pain freedom at 6-months following treatment per the Brief Pain Inventory;
- 6-month local control, defined as an actuarial 6-month rate of any new, recurrent or progressing (as defined by SPINO criteria) tumor within the planning target volume on any post-treatment MRI by 6 months. Follow-up MRIs will be fused with the planning scan for this assessment
- 6-month vertebral compression fracture rate, assessed by post-treatment MRI by 6 months;
- 6-month overall survival;
- 12-month vertebral compression fracture rate, assessed by post-treatment MRI at 12 months;
- demographic disparities (by race, ethnicity, sex, insurance status) in spine SBRT access and outcomes at 3 months;
- demographic disparities (by race, ethnicity, sex, insurance status) in spine SBRT access and outcomes at 6 months.

Study design

This is a prospective, real-world randomized trial to determine the optimal spine SBRT regimen (no SBRT, one fraction SBRT, or two-fraction SBRT) for achieving pain freedom at 3 months in subjects with a diagnosis of spine metastatic disease from MRI and tissue diagnosis of primary malignancy.

Study design including dose escalation/cohorts

Subjects will be randomized to standard-of-care SBRT (24 Gy in 2 fractions), one-fraction SBRT (19 Gy in 1 fraction) or conventional EBRT (8 Gy in 1 fraction). Subjects will be randomized in a 2:1 distribution between the SBRT and EBRT arms.

Number of subjects

Approximately 240 subjects will be enrolled in this trial.

Replacement of subjects

If a subject fails to complete SBRT/EBRT as prescribed, they will be replaced.

Expected duration of treatment and subject participation

Expected duration of treatment approximately one month including screening CT simulation followed by one (EBRT and one-fraction SBRT) or two (standard-of-care SBRT) days of treatment. Follow up for all patients is twelve months. Thus, the duration of subject participation is thirteen months.

Eligibility criteria

Inclusion criteria

1. Histologically or cytologically confirmed spinal metastatic disease
2. No previous radiation therapy encompassing the anatomic site to be treated with spine SBRT.
3. Age ≥ 18 years. This study requires informed consent by the subject; as children are not able to perform this without parental approval, subjects < age 18 are excluded from this study.
4. Life expectancy of ≥ 3 months, in the opinion of and as documented by the investigator.
5. Subject must have a worst pain score ≥ 2 of 10 according to the Brief Pain Inventory.
6. Subject must have no intention of changing pain medications on the first day of SBRT.
7. Subject must have a Spinal Instability score (SINS) ≤ 12.
8. Subject must be a spine SBRT candidate per Radiation Oncology.
9. Subject must have the ability to understand and the willingness to sign a written informed consent document.

Inclusion of women and minorities

Men, women and members of all races and ethnic groups are eligible for this trial. The goals for SPORTSMEN accrual of patients from groups underrepresented in medicine is for racial and ethnic demographics to mirror those of the US Census, which for African-Americans is 12.6% representa-

tion [29]. Furthermore, the principal investigator is also the creator of the Navigator-Assisted Hypofractionation (NAVAH) program utilizing patient navigation to increase underrepresented minority patient access to short-course radiation therapy to reduce radiation therapy access disparities; this program will assist in ensuring the SPORTSMEN trial actively recruits a diverse and representative patient population [30, 31].

Treatment plan

The SBRT fractionation schema (comprising 2 of the 3 arms of the study) will be specified as one of the options noted in Table 1. Following randomization, all patients will be treated to their assigned fractionation schema to completion.

Food and Drug Administration (FDA)-approved stereotactic localization procedures for imaging and treatment delivery will be used for linear accelerator based stereotactic localization with an immobilization system, and similarly for proton-based stereotactic localization. The dose will be prescribed to the isodose surface, which encompasses the margin of the metastasis, as defined by the imaging studies. The 100% dose will be recorded for each patient.

For patients with multiple spine metastases, SBRT will be delivered to each lesion that has not previously undergone radiation therapy. The prescribed dose will be according to the SPORTSMEN schema as described in Table 1 above.

If the above constraints cannot be met utilizing the prescribed radiosurgery dose in Table 1, then the highest dose to the target volume will be used such that constraints can be met. This will be considered a minor deviation. The conventional EBRT arm will be treated to 8 Gy × 1.

Radiation therapy

General guidelines and timing

Spine SBRT will be delivered on all patients utilizing linear accelerator or proton-based techniques as per SPORTSMEN dosing criteria

Equipment and techniques to be used

For SBRT, patients will be treated with linear accelerator. For lesions superior to T4, a facemask will be used; those inferior to T4 will not require a facemask, but will require a Pro-Lok type immobilization system. The most recent MRI is to be fused with the CT simulation prior to contouring.

Target volumes

The GTV is defined as the gross disease visible on pre-treatment MRI (when visible). The CTV is defined as the GTV + microscopic disease on CT simulation; of note, a GTV is not required for all treatment plans, a CTV covering the Radiation Oncologist's clinical judgment of disease extent is sufficient. The PTV is defined as setup error. For SBRT, the PTV = CTV + 0.2 cm. For EBRT, the PTV = CTV + 0.7 cm.

Dose to target and organs at risk constraints

Constraints for organs-at-risk will be as per the CCTG/SC24 trial protocol[8] for patients receiving SBRT. Table 2 lists some of the common spine SBRT dose constraints.

Follow-Up

Subjects will be followed approximately every 3 months (± 30 days) after SBRT/EBRT for 6 months. A detailed medical history, toxicity assessment and physical examination including vital signs will be performed at each visit. Each follow-up over this time period will also include a Spine MRI with and without contrast, which will be analyzed per Spine response assessment in Neuro-Oncology (SPINO) criteria (Section 7) for assessment of local control, and for development of vertebral compression fracture. Neurologic status will be assessed using the Neurologic Assessment in Neuro-Oncology (NANO) scale [32].

After the 6-month follow-up period, subjects will be followed according to their treating physician per standard of care every 3-6 months, with the final MRI obtained at 12 months of follow-up. MRI Spine obtained during this time period may be used for assessment of primary and secondary endpoints; however, are not mandated to be obtained at particular time intervals.

Adverse events and potential risks

Reported adverse events of spine SBRT include: spine fracture, spinal cord toxicity (myelopathy), esophageal fistula, bowel dysfunction, fatigue, and secondary cancer formation.

Study parameters and calendar

Study parameters

The following will be completed prior to spine SBRT:

1. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization
2. Diagnostic MRI Spine, performed per institutional standard of care
3. Medical history and clinical examination performed by radiation oncology, neurosurgery, medical oncology and/or neuro-oncology
4. Baseline ds-GPA.

Calendar

The SPORTSMEN calendar is depicted in Table 3.

Measurement of efficacy

Local progression will be defined according to the SPIne response assessment in Neuro-Oncology (SPINO) group and will consist of at least one of the following [31–34]:

1. Gross unequivocal increase in volume or linear dimension.
2. New or progressive tumor in the epidural space.
3. Neurological deterioration attributable to pre-existing epidural disease dimensions specific to the target volume site.

Results

Statistical methods

General considerations

The overarching aim of this study is to assess and compare the safety and efficacy of two regimens for treating symptomatic metastatic neoplasms: 24 Gy in 2 fractions and 19 Gy in 1 fraction in the SBRT arm, and 8 Gy in 1 fraction in the EBRT arm. The 24 Gy/2 fx regimen has been validated with Level I evidence [8]. The primary endpoint is 3-month pain-free rates post-treatment. Other safety and efficacy endpoints will be assessed as secondary. The statistical analysis methods are outlined below.

Study design

This is a phase 2, open-label, randomized control trial with 3 arms. Eligible patients will be ran-

Table 3. The Spine Patient Optimal Radiosurgery Treatment for Symptomatic Metastatic Neoplasms (SPORTSMEN) study calendar

	Baseline screening	SBRT	3 month follow up[1]	6 month follow up[1]	9 month follow up	12 month follow up[2]
	Within 30 days of SBRT	Linear Accelerator (LINAC) or Proron	90 days post SBRT	180 days post SBRT	270 days post SBRT	360 days post SBRT
Radiation oncology consult and consent	x					
Medical history (including Brief Pain Inventory score)	x		x	x	x	x
Physical examination	x		x	x	x	x
Vitals	x	x	x	x	x	x
ds-GPA/ECOG performance status/KPS	x		x	x	x	x
Diagnostic MRI spine	x					
MRI spine planning scan[4]		x				
Toxicity assessment			x	x	x	x
MRI spine with and without contrast[3]			x	x	x	x

[1]Variations of ± 14 days from the scheduled visits are permitted. [2]After 12-months post-SERT, subjects will be followed at physician's discretion, approximately every 3–6 months per standard of care. Any MRI Spine, physical exam or vitals obtained at these appointments will be gathered. However, if these procedures are not performed per standard of care, this will not be a deviation. [3]MRI spine performed at University Hospitals Cleveland Medical Center will have sequences including contrast, no contrast, FLAIR, DTI and PWI. If patient receives MRI spine outside of University Hospitals Cleveland Medical Center, a minimum of contrast, no contrast and FLAIR will need to be obtained and all sequences mentioned above are encouraged. [4]Variations of –30 days from the scheduled visit are permitted for SBRT, and may include the baseline screening MRI at the treating radiation oncologist's discretion. SBRT — stereotactic body radiation therapy; ds-GPA — disease-specific Graded Prognostic Assessment Scale; ECOG — Eastern Cooperative Oncology Group; KPS — Karnofsky Performance Status; MRI — magnetic resonance imaging

domized with equal probability to standard-of-care SBRT arm (24 Gy in 2 fractions), one-fraction SBRT arm (19 Gy in 1 fraction) versus the EBRT arm (8 Gy in 1 fraction).

Analysis Datasets

Enrolled population — the enrolled population comprises all subjects who meet the eligibility criteria and are registered onto the study.

Safety population — the safety population comprises all subjects who have received at least one dose of radiation. This set will be used for safety analysis.

Efficacy population — The efficacy population comprises all subjects who have completed SBRT or EBRT. This population will be used for efficacy analysis.

Sample size

The planned accrual is 240 evaluable patients. We assume the 3-month pain-free rates of the two SBRT arms will be the same. The power analysis is based on our primary hypothesis that the 3-month pain-free rate of the combined SBRT arm is superior to EBRT. Based on literature, we assume that the 3-month pain-free rates are 30% for SBRT and 15% for EBRT. A sample size of 218 patients (64 patients per arm) provides 80% power to detect such an effect size using a 0.05 level, one-sided two-sample proportion test, while accounting for a formal interim analysis for efficacy. Based on our experience, we aim to enroll up to 60 patients each year at University Hospitals and contributing centers. The patient accrual is expected to be completed within the first two years.

Interim analyses

For this study, it is planned that the Data Safety and Monitoring Board (DSMB) will review safety data on a regular frequency, e.g., every six months. DSMB may request additional safety data review. Such safety analyses do not inflate the type I error for the primary hypothesis testing and thus require no multiplicity adjustments. No formal interim safety analyses are planned.

We will conduct an interim analysis at 3 months after 50% (or 120) patients complete RT. A one-sided group sequential design will be used at the interim analysis using a Hwang-Shih-DeCani spending function at 50% of the information. The critical p-values (boundaries) for rejecting the null (efficacy) or alternative hypothesis (futility) are 0.0009 and 0.9731 at interim analysis and are 0.0499 and 0.9094 at final analysis. If the test for primary endpoint does not cross the pre-specified boundaries at the interim analysis, a final efficacy and safety analysis will occur after all participants complete the study follow-up. In parallel, we will also compare the 3-month pain-free rates between the two SBRT arms, which requires no multiplicity adjustments.

If the test statistic of the interim analysis for the primary endpoint crosses the pre-specified efficacy boundary, the study will drop the EBRT arm, but will continue enrolling the two SBRT arms. Under the unlikely scenario when one SBRT arm is inferior, we will exclude that SBRT arm with excessive pain-free rate, and continue with the other two arms. Results of the interim analysis will be presented to the DSMB by the study team.

Patient characteristics and significant protocol violations

Baseline subject characteristics will be tabulated, such as demographics (age, race, gender), and disease characteristics [disease-specific Graded Prognostic Assessment scale (ds-GPA)].

Disposition

The reasons for patient treatment and study discontinuation will be summarized.

Analysis of primary objectives

The primary endpoint of 3-month pain-free rate post-SBRT/EBRT will be calculated as the proportion of patients who reported pain freedom at 3 months in the Brief Pain Inventory along with a 95% confidence interval. The calculation will take place in the combined SBRT arm and the EBRT arm. Two-sample proportion test will be used to compare the combined SBRT arm *vs.* EBRT arm. A two-tailed, multivariable logistic regression model will be used to assess the effect of treatment regimen on pain events, where the outcome is whether a patient is free from pain at 3 months (yes/no), and the independent variables include treatment arm (SBRT *vs.* EBRT) and baseline covariates for potential efficiency gain. The estimated effect will be reported as odds ratio (OR, SBRT *vs.* EBRT) with 95% CI.

To further compare the two SBRT regimens, we will calculate the 3-month pain-free rates separately for each SBRT regimen. Two-sample proportion test and two-tailed multivariable logistic regression will be used to compare the two regimens and quantify the effect.

Analysis of secondary objectives

The 6-month pain-free rate will be analyzed similarly as in Section 12.8. Other secondary endpoints, including local control, vertebral compression fracture, and overall survival will be estimated using the Kaplan-Meier methods, where the time to events will be calculated as the duration from randomization to the corresponding event of interest. Patients without the corresponding event of interest will be censored at their last clinical follow-up. Log-rank test will be used to compare the regimens. Multivariable Cox regression models will be used to quantify the effect of RT regimens on these time-to-event endpoints, while adjusting for baseline covariates as specified in Section 12.8. The aforementioned analyses will be performed to compare 1) combined SBRT *vs*. EBRT and 2) three-arm comparison. The proportional hazard assumption will be assessed by visualizing and testing Schoenfeld residuals.

To assess the disparities in outcomes, including pain-free rates and other secondary endpoints, descriptive statistics will be summarized stratified by groups defined using race, ethnicity, sex and insurance status. Two-sample tests (proportion tests for rates, and log-rank tests for time-to-event outcomes) or their multi-group extensions will be used for marginal comparisons between these groups. Regression models (logistic regression or Cox proportional hazard model) will be used to quantify the difference between these groups while adjusting for baseline covariates.

Discussion

This is the first phase II to objectively assess optimal spine SBRT dosing in the treatment of symptomatic spine metastatic disease, while assessing the efficacy of spine SBRT versus EBRT. This will also be the first neuro-oncology trial to prospectively target recruitment of underrepresented minorities to ensure participation commensurate with US Census representation.

Conclusions

Findings should allow for better determination of the efficacy of two-fraction spine SBRT versus EBRT in the United States, as well as for the novel single-fraction 19 Gy spine SBRT regimen in patients with symptomatic spine metastases. Furthermore, the commitment of this trial to diversity, equity and inclusion from its inception will allow for increased access to standard-of-care treatment of metastatic spine disease regardless of patient race, ethnicity, gender or socioeconomic status.

Conflicts of interest

Dr. McClelland serves as a consultant for Gilmartin Capital (a company that evaluates surgically targeted radiation therapies), receives travel funding from GT Medical Technologies Inc., and receives research funding from the University Hospitals Minority Faculty Career Development Award, the ASTRO Emerging Investigator Award, the Robert Winn Diversity in Clinical Trials Career Development Award, and the National Cancer Institute Paul Calabresi K12 Clinical Oncology Research Career Development Program. Dr. Spratt receives research funding from the National Institutes of Health and the Prostate Cancer Foundation and personal fees from Astellas, AstraZeneca, Bayer, BlueEarth, Boston Scientific, Elekta, GT Medical Technologies Inc., Myovant, Pfizer, Janssen, Novartis, and Varian.

Funding

This trial is funded by the Robert Winn Diversity in Clinical Trials Career Development Award.

Author contributions

Conception and design: S.McC., Y.S., D.E.S.; manuscript writing: S.McC.; study coordination: S.McC. Participating centers: University Hospitals Seidman Cancer Center Case Western Reserve University School of Medicine, Cleveland, OH 44106
Final approval of manuscript: All authors

References

1. Gerszten PC. Spine metastases: from radiotherapy, surgery, to radiosurgery. Neurosurgery. 2014; 61 Suppl 1:16-25(Suppl 1): 16–25, doi: 10.1227/NEU.0000000000000375, indexed in Pubmed: 25032525.

2. Ho JC, Tang C, Deegan BJ, et al. The use of spine stereotactic radiosurgery for oligometastatic disease. J Neurosurg Spine. 2016; 25(2): 239–247, doi: 10.3171/2016.1.SPINE151166, indexed in Pubmed: 27035507.
3. Perrin RG, Laxton AW. Metastatic spine disease: epidemiology, pathophysiology, and evaluation of patients. Neurosurg Clin N Am. 2004; 15(4): 365–373, doi: 10.1016/j.nec.2004.04.018, indexed in Pubmed: 15450871.
4. Kim E, McClelland S, Jaboin JJ, et al. Disparities in Patterns of Conventional Versus Stereotactic Body Radiotherapy in the Treatment of Spine Metastasis in the United States. J Palliat Care. 2021; 36(2): 130–134, doi: 10.1177/0825859720982204, indexed in Pubmed: 33356987.
5. Hamilton AJ, Lulu BA, Fosmire H, et al. Preliminary clinical experience with linear accelerator-based spinal stereotactic radiosurgery. Neurosurgery. 1995; 36(2): 311–319, doi: 10.1227/00006123-199502000-00010, indexed in Pubmed: 7731511.
6. Pan H, Rose BS, Simpson DR, et al. A survey of stereotactic body radiotherapy use in the United States. Cancer. 2011; 117(19): 4566–4572, doi: 10.1002/cncr.26067, indexed in Pubmed: 21412761.
7. McClelland S, Kim E, Passias PG, et al. Spinal stereotactic body radiotherapy in the United States: A decade-long nationwide analysis of patient demographics, practice patterns, and trends over time. J Clin Neurosci. 2017; 46: 109–112, doi: 10.1016/j.jocn.2017.08.007, indexed in Pubmed: 28864408.
8. Sahgal A, Myrehaug SD, Siva S, et al. trial investigators. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncol. 2021; 22(7): 1023–1033, doi: 10.1016/S1470-2045(21)00196-0, indexed in Pubmed: 34126044.
9. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap. 1994; 23(2): 129–138, indexed in Pubmed: 8080219.
10. McClelland S, Deville C, Thomas C, et al. An overview of disparities research in access to radiation oncology care. J Radiat Oncol. 2016; 5(4): 437–444, doi: 10.1007/s13566-016-0284-1.
11. McClelland S, Page BR, Jaboin JJ, et al. The pervasive crisis of diminishing radiation therapy access for vulnerable populations in the United States, part 1: African-American patients. Adv Radiat Oncol. 2017; 2(4): 523–531, doi: 10.1016/j.adro.2017.07.002, indexed in Pubmed: 29204518.
12. McClelland S, Leberknight J, Guadagnolo BA, et al. The pervasive crisis of diminishing radiation therapy access for vulnerable populations in the United States, part 2: American Indian patients. Adv Radiat Oncol. 2018; 3(1): 3–7, doi: 10.1016/j.adro.2017.08.010, indexed in Pubmed: 29556572.
13. McClelland S, Perez CA. The pervasive crisis of diminishing radiation therapy access for vulnerable populations in the United States-part 3: Hispanic-American patients. Adv Radiat Oncol. 2018; 3(2): 93–99, doi: 10.1016/j.adro.2017.12.003, indexed in Pubmed: 29904731.
14. McClelland S, Kaleem T, Bernard ME, et al. The pervasive crisis of diminishing radiation therapy access for vulnerable populations in the United States-Part 4: Appalachian patients. Adv Radiat Oncol. 2018; 3(4): 471–477, doi: 10.1016/j.adro.2018.08.001, indexed in Pubmed: 30370344.
15. McClelland S. When Numbers Lie: The Lessons the True Hurricane Maria Death Toll Should Teach Us About the Necessity of Addressing Radiation Therapy Access Disparities in the United States. Int J Radiat Oncol Biol Phys. 2018; 102(3): 672–673, doi: 10.1016/j.ijrobp.2018.06.029, indexed in Pubmed: 30174133.
16. Tseng CL, Soliman H, Myrehaug S, et al. Imaging-Based Outcomes for 24 Gy in 2 Daily Fractions for Patients with de Novo Spinal Metastases Treated With Spine Stereotactic Body Radiation Therapy (SBRT). Int J Radiat Oncol Biol Phys. 2018; 102(3): 499–507, doi: 10.1016/j.ijrobp.2018.06.047, indexed in Pubmed: 30003994.
17. Murray Brunt A, Haviland JS, Wheatley DA, et al. FAST-Forward Trial Management Group. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020; 395(10237): 1613–1626, doi: 10.1016/S0140-6736(20)30932-6, indexed in Pubmed: 32580883.
18. McClelland S. Breast cancer radiation therapy. Lancet. 2020; 396(10262): 1559, doi: 10.1016/S0140-6736(20)32324-2, indexed in Pubmed: 33189174.
19. Huo M, Sahgal A, Pryor D, et al. Stereotactic spine radiosurgery: Review of safety and efficacy with respect to dose and fractionation. Surg Neurol Int. 2017; 8: 30, doi: 10.4103/2152-7806.200581, indexed in Pubmed: 28303210.
20. Leeman JE, Bilsky M, Laufer I, et al. Stereotactic body radiotherapy for metastatic spinal sarcoma: a detailed patterns-of-failure study. J Neurosurg Spine. 2016; 25(1): 52–58, doi: 10.3171/2015.11.SPINE151059, indexed in Pubmed: 26943256.
21. Lee MY, Ouyang Zi, LaHurd D, et al. A Volumetric Dosimetry Analysis of Vertebral Body Fracture Risk After Single Fraction Spine Stereotactic Body Radiation Therapy. Pract Radiat Oncol. 2021; 11(6): 480–487, doi: 10.1016/j.prro.2021.07.004, indexed in Pubmed: 34303836.
22. Sahgal A, Atenafu EG, Chao S, et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. J Clin Oncol. 2013; 31(27): 3426–3431, doi: 10.1200/JCO.2013.50.1411, indexed in Pubmed: 23960179.
23. Rose PS, Laufer I, Boland PJ, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. J Clin Oncol. 2009; 27(30): 5075–5079, doi: 10.1200/JCO.2008.19.3508, indexed in Pubmed: 19738130.
24. Yamada Y, Katsoulakis E, Laufer I, et al. The impact of histology and delivered dose on local control of spinal metastases treated with stereotactic radiosurgery. Neurosurg Focus. 2017; 42(1): E6, doi: 10.3171/2016.9.FOCUS16369, indexed in Pubmed: 28041329.
25. Palma DA, 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(10185): 2051–2058, doi: 10.1016/S0140-6736(18)32487-5, indexed in Pubmed: 30982687.
26. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of

Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. J Clin Oncol. 2020; 38(25): 2830–2838, doi: 10.1200/JCO.20.00818, indexed in Pubmed: 32484754.
27. Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the epidural spinal cord compression scale. J Neurosurg Spine. 2010; 13(3): 324–328, doi: 10.3171/2010.3.SPINE09459, indexed in Pubmed: 20809724.
28. US Census Bureau. Overview of Race and Hispanic Origin: 2010. https://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf (March 10, 2018).
29. McClelland S, Petereit DG, Zeitlin R, et al. Improving the Clinical Treatment of Vulnerable Populations in Radiation Oncology. Adv Radiat Oncol. 2020; 5(6): 1093–1098, doi: 10.1016/j.adro.2020.07.018, indexed in Pubmed: 33305069.
30. McClelland S, Harris EE, Spratt DE, et al. Navigator-assisted hypofractionation (NAVAH) to address radiation therapy access disparities facing African-Americans with breast cancer. Rep Pract Oncol Radiother. 2022; 27(3): 583–588, doi: 10.5603/RPOR.a2022.0064, indexed in Pubmed: 36186700.
31. Thibault I, Chang EL, Sheehan J, et al. Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. Lancet Oncol. 2015; 16(16): e595–e603, doi: 10.1016/S1470-2045(15)00166-7, indexed in Pubmed: 26678212.
32. Nayak L, DeAngelis LM, Brandes AA, et al. The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. Neuro Oncol. 2017; 19(5): 625–635, doi: 10.1093/neuonc/nox029, indexed in Pubmed: 28453751.
33. Laufer I, Lo SS, Chang EL, et al. Population description and clinical response assessment for spinal metastases: part 2 of the SPIne response assessment in Neuro-Oncology (SPINO) group report. Neuro Oncol. 2018; 20(9): 1215–1224, doi: 10.1093/neuonc/noy047, indexed in Pubmed: 29590465.
34. Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. Int J Radiat Oncol Biol Phys. 2008; 71(3): 652–665, doi: 10.1016/j.ijrobp.2008.02.060, indexed in Pubmed: 18514775.