Title: Adaptive Staged Stereotactic Body Radiation Therapy in Treating Patients With Spinal Metastases That Cannot Be Removed by Surgery
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PI: **Madhur Garg**

Adaptive High-Dose Radiotherapy for Metastatic Epidural Disease in the Spine

CONFIDENTIAL

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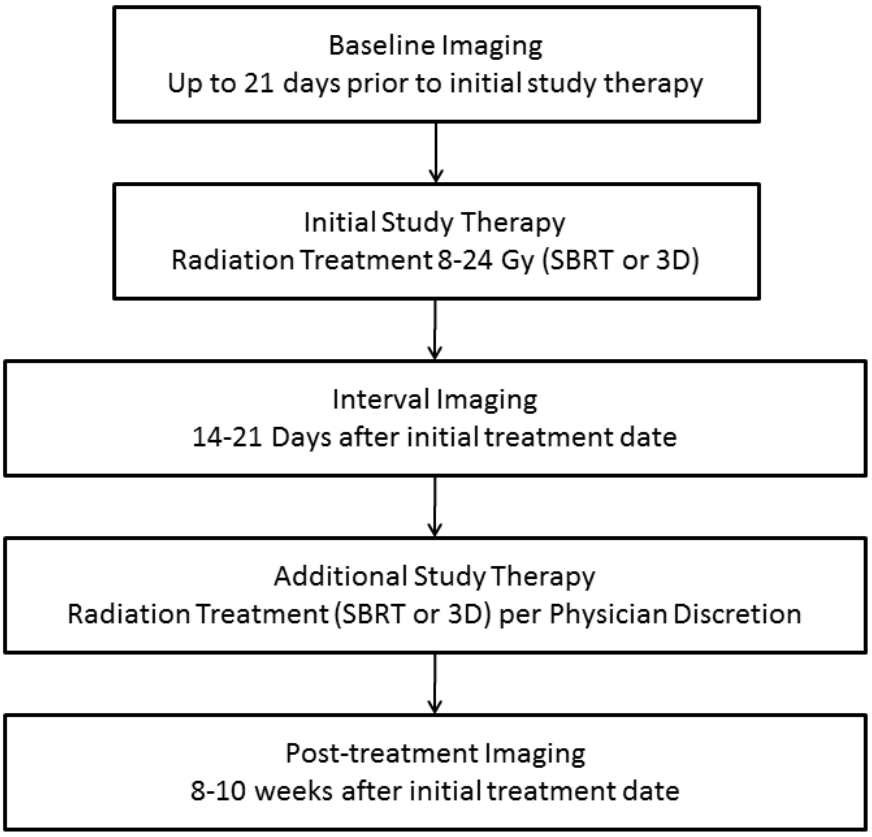
Adaptive Staged SBRT for Spinal Metastases

SCHEMA



Sample size: 15 patients

Abbreviations

ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ANC	Absolute neutrophil count
AUC	Area under the curve
BID	Twice daily
BSA	Body surface area
chemoRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTV	Clinical Target Volume
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
EQD2	Equivalent dose in 2-Gy fractions
Fx	Fractions
FDG	Fludeoxyglucose
GFR	Glomerular filtration rate
GTV	Gross tumor volume
Gy	Gray
IMRT	Intensity modulated radiotherapy
IV	Intravenous
LA-NSCLC	Locally-advanced non-small cell lung cancer
LD	Longest diameter
LLN	Lower limit of normal
LRC	Locoregional control
MRI	Magnetic Resonance Imaging
MESCC	Metastatic Epidural Spinal Cord Compression
OS	Overall survival

PET	Positron emission tomography
PHI	Protected health information
PI	Principal investigator
PO	By mouth
PTV	Planning target volume
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
RTOG	Radiotherapy Oncology Group
Rx	Prescription
SAE	Serious adverse event
SBRT	Stereotactic Body Radiation Therapy
SUV	Standardized uptake value
ULN	Upper limit of normal
VMAT	Volumetric modulated arc therapy

Contents

1.0 OBJECTIVES

1.1 Primary Objective

To assess the feasibility of single-fraction radiotherapy to provide a short-interval treatment response in patients with MESCC, such that radiographic decompression is achieved, or additional stereotactic radiotherapy to full therapeutic doses can be delivered while respecting spinal cord constraints, based on the following metrics:

- Shortest distance between gross disease and the spinal cord before and after treatment
- Epidural tumor volume before and after treatment
- Extent of epidural compression before and after treatment

1.2 Secondary Objectives

To evaluate pain control using the Numerical Rating Pain Scale (NRPS) before and after treatment

To evaluate patient quality of life using the Functional Assessment of Cancer Therapy-General (FACT-G) before and after treatment

To evaluate functional outcomes using ambulation score and standardized neurologic exams before and after treatment

2.0 BACKGROUND

2.1 Spinal Cord Compression

Metastatic epidural spinal cord compression (MESCC) is a relatively rare but serious complication of cancer occurring in approximately 5% of diagnosed patients (and can be the presenting symptom in up to 20% of undiagnosed cases). It is a medical emergency, which if not addressed, can lead to permanent neurologic deficits including paraplegia. Although patients with this presentation often do poorly (median survival is estimated at between 3-6 months), there are prognostic indicators of improved outcomes including the preservation of ambulation ability, radiosensitive tumor histology, low systemic extent of disease, and single involved region of the spine [1].

Prompt diagnosis and treatment using a multidisciplinary approach has now become the standard of care. Diagnosis is aided by clinical suspicion based on presenting symptoms, with the most common including back pain, motor deficits, sensory deficits and autonomic dysfunction. Approximately 60% of patients remain ambulatory at presentation [2]. Diagnosis is confirmed radiographically with MRI being the current method of choice (sensitivity and specificity of up to approximately 93% and 98% respectively) [3].

First line therapy for MESCC begins with corticosteroids to reduce edema and provide cytoreductive effects on some sensitive histologies [4]. Until recently, the standard of care for patients was conventional fractionated radiotherapy delivered on an emergent basis. However, a prospective randomized study in 2005 by Patchell et al demonstrated that immediate surgical decompression for a subset of patients followed by adjuvant radiation conferred a number of benefits when compared to radiation therapy alone [5]. Patients preserved the ability to ambulate (84% vs. 57%, p=0.001) and more regained this ability (10 patients vs. 3 patients). Furthermore, those patients undergoing surgery had improved survival times (median 126 days vs. 100 days, p=0.003). The key conclusion from this study was that when used judiciously on a carefully selected cohort of patients, surgical decompression can provide a viable alternative to definitive radiotherapy. These criteria include a non-radiosensitive or unknown primary histology, single area of compression, symptoms present no longer than 48 hours, or relapsed or progression of disease while receiving radiotherapy [1]. It is estimated that 10-15% of patients are appropriate candidates for surgery [2].

For the majority of patients that do not meet the aforementioned criteria or who are poor surgical candidates due to medical comorbidities or other factors, the correct treatment approach is an open question. Definitive radiotherapy remains the standard of care with or without corticosteroids, however there has been no clear demonstration of the effectiveness of conventional treatment for improving neurologic function in patients with MESCC, among several tested dosing regimens [2]. In this pilot study, we plan to evaluate the use of staged high-dose radiotherapy for patients with MESCC, to determine if a treatment response can be observed within a short enough interval to improve symptoms or provide additional radiotherapy safely. We will utilize SBRT where possible as this technique has shown promise in providing disease and symptomatic control to date.

2.2 Conventional Radiotherapy

Conventional radiotherapy has historically been the standard of care and remains the most common treatment of MESCC [2]. There have been several randomized trials regarding the optimal dosing regimen in these patients, however none has been found to be significantly effective in improving functional outcomes.

An early example analyzed 276 patients with MESCC comparing two hypofractionated regimens; sequential single-fraction dosing (8 Gy x 2 on days 1 and 8) vs. a split-course regimen (5 Gy x 3, 4-day treatment break, followed by 3 Gy x 5). They found no difference in pain control or post-treatment motor function, with ambulation preserved in approximately 70% in both groups [6]. A larger retrospective comparison from the same year reviewed 1,304 patients comparing five distinct regimens (8 Gy x 1, 4 Gy x 5, 3 Gy x 10, 2.5 Gy x 15, and 2 Gy x 20), and also found no difference in functional outcomes, however noted that local control was improved in the longer courses. Notably, a multivariate analysis identified several factors aside from the treatment regimen that influenced functional outcomes, including age, performance status, tumor histology, number of spinal cord lesions, ambulatory status and interval to treatment [7].

These results were further corroborated by a non-randomized prospective trial including 265 patients with MESCC, comparing a short-course regimen (8 Gy x 1 or 4 Gy x 5) to a long-course (3 Gy x 10, 2.5 Gy x 15, or 2 Gy x 20). The authors found that the radiation schedule had no significant impact on functional outcomes based on univariate analysis (performance status, tumor type, number of vertebrae involved, ambulatory status prior to treatment, and time to symptoms were all significant), though long-courses were associated with improved local control [8]. A systematic review and clinical practice guideline recently recommended that for non-surgical patients, those with poor prognoses should receive 8 Gy x 1, whereas those with more favorable prognoses should be treated with 3 Gy x 10 [4]. It should be reiterated that improvement of motor function was observed in only 28% of patients after shortcourse radiotherapy and in 29% of patients after longercourse radiotherapy, indicating neither is effective for this purpose. Further progression of motor deficits was prevented in 56% and 55% of patients, respectively.

Most recently, another prospective randomized trial comparing 10 Gy x 1 vs. 4 Gy x 5 for patients with MESCC again found both groups performed similarly without a noted improvement in neurologic outcomes [ASTRO 2014]. Improvement in mobility status was even less impressive, occurring in only 10.5% of patients on each arm while improvement in bladder control occurred in 2.6 to 10.5% of patients. Although the 10 Gy arm was not inferior to the 20 Gy arm, this study again showed that conventional definitive radiotherapy had a poor vital and functional prognosis overall.

Currently 10 Gy x 1 using conventional techniques remains an option based on existing clinical data. However, there is clearly a need for a more effective treatment for patients with MESCC who cannot undergo surgery.

2.3 SBRT for Spinal Cord Compression

Within the last 10 years, the use of stereotactic body radiation therapy (SBRT) has shown increasing promise in treating spine metastases. A number of retrospective and prospective studies have demonstrated effective local and symptomatic control.

A small retrospective series from Yamada et al initially demonstrated that stereotactic treatment or retreatment of paraspinal lesions up to 70 Gy could be achieved safely using non-invasive body frames. 35 patients underwent treatment with 90% reporting palliation of pain or parasthesias with local control rates of 75-81% [9]. Notably there were no cases of radiation induced myelopathy indicating high-dose per fraction was possible while respecting spinal cord constraints. A larger phase I-II study of spine SBRT then reported on treatment of 63 patients (74 metastatic lesions) with 27-30 Gy in 3-6 fractions. Similarly, they noted 1-year local control rates of 84% [10]. A much larger cohort of 500 patients were prospectively followed by Gertszten et al after receiving single fraction doses of 12.5 o 25 Gy. Long-term pain control was consistent with previous findings of 86%, with local control reported at 90%. Further, 84% of patients with a progressive deficit reported some clinical improvement [11].

Although these findings and others support the use of SBRT for local and symptomatic control for spinal metastases, patients with MESCC present a unique problem of the tumor abutting the thecal sac and cord directly, potentially limiting its application while respecting constraints on the spinal cord dose. In these cases, a therapeutic dose of16-24 Gy in 1-3 fractions often cannot safely be delivered.

More recently, a prospective clinical trial reported on the effectiveness of SBRT for patients with MESCC, as measured by the reduction of epidural tumor volume and improvement in thecal sac patency. They enrolled 62 patients with MESCC who were treated with 14-20 Gy in a single fraction. The results demonstrated a 64% reduction of the epidural tumor volume at 2 months following treatment, with 80% of the patients also showing improvement in thecal sac patency. Notably, however, 16% of these patients had neurologic progression (9/62 patients). Of these 9 patients, 5 had decompressive surgery thereafter in which 2 showed necrosis, 2 died from intraoperative complications and 1 had tumor progression [12]. This trial indicated that a radiographic response can be observed rapidly, however there is clearly a risk of neurological toxicity from delivering single doses of 14 Gy or higher to tumors abutting the spinal cord.

Previous studies have estimated spinal cord constraints ranging from 10-14 Gy for single fraction SBRT treatments [10, 13, 14]. RTOG 0631, an ongoing prospective randomized trial which investigated the use of SBRT for palliation of spine metastases (16 Gy SBRT vs. 8 Gy x 1 conventional), applied these constraints using 10 Gy to 10% of the spinal cord (cross sectionally) to a maximum of 6mm above and below the target volume, and max dose of 14 Gy. However, patients are excluded if there was frank epidural compression within 3 mm of the spinal cord.

Based on the above findings, we are proposing a trial for patients with inoperable MESCC utilizing adaptive planning and a staged application of radiotherapy. Such an approach can potentially deliver therapeutic doses to the tumor while respecting the established spinal cord constraints. We hypothesize that a single fraction of treatment may induce a short-interval radiographic response (within approximately 2-3 weeks), which can then be used to plan an additional treatment if needed. The response may

also allow us to achieve therapeutic dose levels by reducing the volume of overlap with the spinal cord. We will also observe the radiographic response from high-dose single fraction regimens if decompression can be achieved in this fashion.

3.0 PATIENT ELIGIBILITY

Patients will be recruited via physician referral. Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. The eligibility checklist must be completed on the case report form and maintained in each patient's chart.

3.1 Inclusion Criteria

Localized spine metastasis from the C1 to L5 levels with documented epidural extension or spinal cord compression by a diagnostic imaging study (MRI, diagnostic CT, or CT myelogram recommended). Site(s) may have a maximal involvement of 3 contiguous vertebral bodies. Patients with other visceral metastasis, and radioresistant tumors (including soft tissue sarcomas, melanomas, and renal cell carcinomas) are eligible.

History/physical examination by the treating physician within 7 days prior to study therapy

Neurological and functional examination within 7 days prior to study therapy by the treating physician (see Appendix D).

Negative serum pregnancy test

Age $\geq$ 18

Diagnostic Imaging (MRI with gadolinium is recommended, other modalities include CT myelogram or diagnostic CT with iodinated contrast) of the involved spine within 21 days prior to initial study therapy to determine the extent of the spine involvement

Numerical Rating Pain Scale within 7 days prior to study therapy; Documentation of the patient's initial pain score is required. Patients taking medication for pain at the time of registration are eligible.

Women of childbearing potential must:

- Have a negative serum or urine pregnancy test within 1 week prior to the start of study therapy
- Agree to utilize an adequate method of contraception throughout treatment and for at least 4 weeks after study therapy is completed
- Be advised of the importance of avoiding pregnancy during trial participation and the potential risks of an unintentional pregnancy.

All patients must sign study specific informed consent prior to study entry or within 1 week of first treatment, provided other criteria were met.

Patients considered for enrollment are strongly recommended to have been discussed at multidisciplinary tumor board with input from surgery, medical oncology and radiation oncology prior to enrollment.

3.2 Exclusion Criteria

Histologies of myeloma or lymphoma

Candidates planned for surgical decompression

Spine instability as determined by SINS score >12 [15]

Compression fracture identified by > 50% loss of vertebral body height

Bony retropulsion at the index spine as predominant cause of epidural extension or cord compression

Prior radiation to the spinal cord at the index spine where the composite dose (including study treatment) would exceed documented constraints

4.0 STUDY DESIGN

4.1 General Design

Treatment

This will be a pilot study assessing the feasibility of staged radiotherapy and adaptive planning on the management of inoperable epidural extension or spinal cord compression (documented by diagnostic imaging). All patients should be started on dexamethasone unless medically contraindicated and dosed per institution guidelines. Initial treatment after evaluation and registration will consist of an initial fraction of 8-24 Gy delivered using a SBRT or 3D conformal approach to the affected region(s). The patients will be re-imaged within 14-21 days by the same modality as diagnosis to assess for radiographic response. If feasible, a second fraction will be delivered at this point per discretion of the treating physician.

Follow-up

Patients will be evaluated with a history, physical examination, pain score, and neurologic assessment at each treatment visit by the treating physician, or more frequently as clinically indicated. Interval diagnostic imaging will be completed 14-21 days after initial treatment to assess response. Thereafter, a third set of diagnostic images will be obtained at 8-10 weeks following initial treatment. Patients will be followed thereafter by the treating physician for survival and recurrence as clinically indicated.

4.2 Study Calendar

	Screening		Treatment	Post-Treatment	
	Day -21 to -1	Day -7 to -1	Day 1	Day 14-21	Week 8-10
History		X		X	X
Physical Exam		X		X	X
SINS Score		X			
Vital Signs & Weight		X		X	X
Neurologic Evaluation		X[A]		X	X
NRPS		X		X	X
ECOG PS		X		X	X
FACT-G		X		X	X
Pregnancy Test		X			
Diagnostic Imaging	X			X	X[C]
Radiation Therapy			X	X[B]	

[A] Appendix D: Neurologic and Functional Assessment.
[B] If indicated, a second fraction will be delivered at this point at the discretion of the treating physician.
[C] should810Follow-up imaging thereafter should occur at the discretion of the treating physician.

3. Primary Endpoint

The primary endpoint of this study is the radiographic response of the spinal tumor, as measured by:

Distance between the gross disease and spinal cord ≥ 3mm after treatment.

A reduction in the epidural tumor volume or thecal sac compression by ≥ 10% after treatment

4.4 Secondary Endpoints

Pain control: Pain scores as measured by the Numerical Rating Pain Scale (NRPS) estimation

Quality of Life: Scores from Functional Assessment of Cancer Therapy (FACT-G)

Ambulation: Based on ambulation score and standardized neurologic exam (Appendix D)

Progression-free survival: the interval from study registration to date of disease progression or death, censored at the date of data collection

Overall survival: the interval from study registration to death, censored at the date of data collection

Grade ≥ 2 radiation-induced lung toxicity, scored using CTCAE, v. 4

Any grade ≥ 3 treatment-related toxicity, scored using CTCAE, v. 4

5.0 RADIOTHERAPY

5.1 Dosimetry

All patients will receive a first fraction of 8 to 24 Gy using a 3D or SBRT technique. The second treatment will be at the discretion of the treating physician and will be based on the clinical parameters, diagnostic interval imaging (2-3 weeks), and achievement of spinal cord dose constraints as described below.

The spinal cord constraints for the first fraction will be a maximum of 9Gy to less than 0.01 cc and 8Gy to less than 0.1 cc volume, respectively. Composite dose constraints(combining both treatments) for the spinal cord area maximum of 18 Gy to less than 0.01 cc and16 Gy to less than 0.1 cc and respectively. Every effort will be made to plan for 90% composite target coverage while keeping the spinal cord dose limits."

If considering a larger single fraction dose (14-16 Gy or above), the constraint should be 12 Gy to less than 0.01cc

5.2 CT simulation, Immobilization and Patient setup

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans should be performed without IV contrast, however may be preceded with a CT myelogram where possible to accurately delineate the spinal cord. Oral contrast may be given. Axial acquisitions with gantry 0 degrees will be required with spacing 1.25-2.5 mm between scans in the region of the tumor. Images will be transferred to the treatment planning computers for treatment planning.

Patients must be positioned in a stable supine position capable for reproducibility of positioning and immobilization from simulation to treatment, allowing the patient to feel as comfortable as possible. The arms should be positioned based on treatment location. Positions uncomfortable for the patient should be avoided to prevent unnecessary movement. A prone position is not allowed. A vacuum bag should be used for immobilization or for cervical spine or cervicothoracic junctional areas, a rigid head and neck immobilization device should be used.

Verification CT scans or portal films prior to each treatment should be taken.

5.3 Target Volumes and Coverage

Image fusion between MRI (gadolinium contrast T1-weighted and T2-weighted images) and simulation CT is recommended for delineation of both the soft tissue tumor

component and the spinal cord. If possible, CT myelogram should be obtained prior to simulation for accurate delineation of the true cord. Special attention (and consideration of deformable registration) should be taken with image fusion when simulation CT and MRI images are taken in different imaging positions.

The gross tumor volume (GTV) should include only the gross disease visible on pre-treatment imaging. A 0-3mm margin expansion is allowed to clinical target volume (CTV), as well as a further 1-2 mm expansion to planning target volume (PTV).

For 3D treatment, the target volume should also be delineated. The treatment field can include a margin of 1-2 cm beyond the vertebral body(s) in any direction, based on the treating physician's discretion, as long as more than or equal to 90% of the target spine volume is covered by the prescription dose.

5.4 Critical Structures

Lung, true cord, esophagus, larynx, brachial plexus, heart/pericardium, kidneys, bowel and liver should be included based on the location of the spinal lesion, and contoured on the published atlases available on the RTOG web site. All critical structures will be outline as detailed in the RTOG 0631 protocol. (http://www.rtog.org/CoreLab/ContouringAtlases.aspx). Dosimetric constraints for organs at risk are listed in **Table 2**. These have been adopted from RTOG 0631.

Cauda Equina	<0.03 cc <5 cc	16 Gy 14 Gy	neuritis
Sacral Plexus	<0.03 cc <5 cc	18 Gy 14.4 Gy	neuropathy
Esophagus*	<0.03 cc <5 cc	16 Gy 11.9 Gy	stenosis/fistula
Ipsilateral Brachial Plexus	<0.03 cc <3 cc	17.5 Gy 14 Gy	neuropathy
Heart/Pericardium	<0.03 cc <15 cc	22 Gy 16 Gy	pericarditis
Great vessels*	<0.03 cc <10 cc	37 Gy 31 Gy	aneurysm
Trachea* and Larynx	<0.03 cc <4 cc	20.2 Gy 10.5 Gy	stenosis/fistula
Skin	<0.03 cc <10 cc	26 Gy 23 Gy	ulceration
Stomach	<0.03 cc <10 cc	16 Gy 11.2 Gy	ulceration/fistula
Duodenum*	<0.03 cc <5 cc	16 Gy 11.2 Gy	ulceration
Jejunum/Ileum*	<0.03 cc <5 cc	15.4 Gy 11.9 Gy	enteritis/obstruction
Colon*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	colitis/fistula
Rectum*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	proctitis/fistula
Renal hilum/vascular trunk	<2/3 volume	10.6 Gy	malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	**Endpoint (≥ Grade 3)**
Lung (Right & Left)	1000 cc	7.4 Gy	Pneumonitis
Renal cortex (Right & Left)	200 cc	8.4 Gy	Basic renal function

*Avoid circumferential irradiation

Table 2 – Dosimetric Constraints

5.5 Radiotherapy Adverse Events

Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely when the pericardium and spinal cord receive doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥ 20 Gy, usually within the

first six months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

6.0 RESPONSE ASSESSMENT

6.1 Primary Endpoint – Radiographic Response

The primary endpoint of this study is achieving radiographic response in the metastatic spinal lesion.

Radiographic response will be achieving 3mm in shortest distance axially between the gross disease and spinal cord at the level where the most severe compression was present, between pre-treatment and interval imaging scans.

Radiographic response will also be achieving a 10% reduction in epidural tumor volume or thecal sac compression between pre-treatment and interval imaging scans. Epidural tumor volume will be estimated by using target volumes contoured before and after treatment by the same practitioner. Thecal sac compression will be estimated using a method adapted from [12]. The thecal sac area at the level of compression is compared to the average value of thecal sacs measured at 1 vertebral body above and below this level. One minus the ratio of the compressed to normal thecal sac area will provide an estimate of the thecal sac compression. These measurements will be taken at the same spine levels to maintain consistency.

Response assessments will be completed by an attending radiation oncologist not directly involved in the patient's clinical care. This approach will preserve objectivity and mirrors an existing peer review process in place for all standard and stereotactic radiation treatments. Collaboration with neuroradiology will also be encouraged during these assessments.

6.2 Secondary Endpoints – NRPS, FACT-G, Ambulation

Secondary endpoints include pain, quality of life and functional outcomes.

For evaluation of pain relief, the Numerical Rating Pain Scale will be used, as done in RTOG 0631. The NRPS is a measure of pain on an 11-point scale (0-10) and has been validated previously on similar cohorts [16].

For quality of life, the Functional Assessment of Cancer Therapy (FACT-G), v. 4.0, also will be collected (also utilized in RTOG 0631). The FACT-G is a commonly used tool measuring quality of life from 4 different perspectives (physical, social, emotional and functional) [17]. It is completed quickly, is accessible to those with varying educational backgrounds, and is available in many languages (http://www.facit.org/translation/translation_landing.aspx).

Functional outcomes and ambulation will be assessed by standard neurologic assessment (Appendix D) by the treating physician.

7.0 STATISTICAL CONSIDERATIONS

7.1 Data Analysis

This pilot study will yield preliminary data on the primary endpoint of distance between gross disease and spinal cord of at least 3mm. Data from the study will be summarized using standard descriptive statistics; formal hypothesis testing will not be performed. Estimates of the treatment effect and standard error on the number of subjects achieving >=3 mm distance will also be used to determine the sample size required for the larger scale study. Therefore, the size of the pilot study should be sufficient to produce reasonably precise estimates of these parameters, where precision is measured by the width of the 95% confidence interval.

The treatment effect will be estimated by p, the observed proportion of patients achieving at least 3 mm distance from the gross disease and spinal cord. Confidence intervals for the true proportion will be computed using Clopper-Pearson exact confidence interval. With 24 subjects and assuming an expected response rate p = 50% produces a two-sided 95% confidence interval with a width equal to 58% (i.e. 21%<=p<=79%). The width shows that the response rate will not be lower than 20%. Since this is a feasibility, study no power calculation is done.

Data regarding secondary endpoints will be reported in a descriptive manner.

8.0 REGULATORY CONSIDERATIONS

8.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

8.2 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to the PI. The PI should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

The investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the PI.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

What protected health information (PHI) will be collected from subjects in this study

Who will have access to that information and why

Who will use or disclose that information

The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has

been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.0 DATA SAFETY AND MONITORING BOARDS

The Albert Einstein College of Medicine/Albert Einstein Cancer Center Data Safety Monitoring Committee (DSMC) has the responsibility for ensuring data and safety monitoring along with the PI who is ultimately responsible for the ongoing monitoring and safety of clinical protocols. The primary functions of the AECC DSMC are as follows:

1. To review and ensure protocol compliance with dose escalation in phase I trials
2. To review/assure protocol compliance for all trials that have two-stage phase II designs,
3. Reviewing all internal and external serious adverse reports, investigator alerts, action letters, and other safety reports for trials being performed at AECC-affiliated institutions and;
4. To implement and to determine the adequacy of DSM plans of all approved protocols.

The DSMC is an independent committee and meets on a monthly basis. During its monthly meeting, the DSMC will review serious (grade 3 or higher) adverse events from this study. In the event that the DSMC decides that a revision is warranted, the committee will immediately notify the principal investigator of this study. The DSMC has the authority to close trials to patient accrual should the risk to patients be excessive or outweigh the potential benefits of the study. All study suspensions and closures will be forwarded to the IRB/CCI and study sponsor from the DSMC.

11.0 ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject and does not necessarily have to have a causal relationship with study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of treatment. During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

AEs will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial intervention or medication. All AEs considered related to trial intervention or medication will be followed until resolution, even if this occurs post-trial.

11.1 Adverse Event Definitions

Adverse Event (AE): any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious Adverse Event (SAE): An AE occurring at any dose that results in any of the following outcomes (CFR 312.32)

Death

Life-threatening adverse experience

Inpatient hospitalization or prolongation of existing hospitalization excluding those for study therapy administration, transfusional support, disease staging/re-staging procedures, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events

Persistent or significant disability or incapacity

Congenital anomaly / birth defect.

The definition of SAE also includes important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive

treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" is that there is a reasonable possibility that the drug or the study intervention caused the adverse experience.

Unexpected Adverse Event: An AE that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening: Any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

AEs will use the descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix B). A list of AEs that have occurred or might occur can be found in sections above.

11.2 Adverse Event Reporting

Study site personnel must notify the PI and the sponsor immediately of any SAE experienced by a patient. In general, SAEs assessed as clearly being due to disease progression, and not due to study drug(s), should be excluded from AE reporting. Study-specific clinical outcomes of death because of disease progression are exempt from SAE reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not an SAE.

The following steps will be taken to report promptly and document accurately any SAE, even if it may not appear to be related to the study treatment:

Report the SAE to the PI and the treating physician by email, telephone or fax within 24 hours of becoming aware that a patient has experienced an SAE.

Record the SAE accurately on the AE page of the patient's CRF.

Using the standard IRB-SAE report form, submit all known patient information within 24 hours of SAE occurrence to the clinical trial office to submit to IRB and DSMB. Date and sign each report before submission. Include the following

information (or as much as possible to obtain and still report the event within 24 hours):

- Study protocol number and indication
- Study site and investigator's identification
- Patient's ID (patient number and initials), age or date of birth, and sex
- Date of enrollment
- Description of SAE, including date of onset and duration, severity, and outcome
- Date of first and most recent (last) dose administered
- Action taken regarding study treatment
- Relationship of SAE to study treatment
- Concomitant medications, including regimen and indication
- Intervention, including concomitant medications used to treat SAE
- Pertinent laboratory data/diagnostic tests conducted and date
- Pertinent medical history of patient
- Date of hospital admission/discharge
- Date of death (if applicable)

Within 10 days of initial IRB notification, the PI is required to submit a completed Adverse Event Report to the IRB. The treating physicians should perform appropriate diagnostic tests and therapeutic measures and submit all follow-up substantiating data, such as diagnostic test reports and autopsy report to the PI, IRB, and DSMB.

12.0 REFERENCES

1. Cole, J.S. and R.A. Patchell, *Metastatic epidural spinal cord compression.* Lancet Neurol, 2008. **7**(5): p. 459-66.
2. Rades, D. and J.L. Abrahm, *The role of radiotherapy for metastatic epidural spinal cord compression.* Nat Rev Clin Oncol, 2010. **7**(10): p. 590-8.
3. Loblaw, D.A., et al., *Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group.* J Clin Oncol, 2005. **23**(9): p. 2028-37.
4. Loblaw, D.A., et al., *A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression.* Int J Radiat Oncol Biol Phys, 2012. **84**(2): p. 312-7.
5. Patchell, R.A., et al., *Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.* Lancet, 2005. **366**(9486): p. 643-8.
6. Maranzano, E., et al., *Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial.* J Clin Oncol, 2005. **23**(15): p. 3358-65.
7. Rades, D., et al., *Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression.* J Clin Oncol, 2005. **23**(15): p. 3366-75.
8. Rades, D., et al., *Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression.* Int J Radiat Oncol Biol Phys, 2011. **79**(2): p. 524-30.
9. Yamada, Y., et al., *Multifractionated image-guided and stereotactic intensity-modulated radiotherapy of paraspinal tumors: a preliminary report.* Int J Radiat Oncol Biol Phys, 2005. **62**(1): p. 53-61.
10. Chang, E.L., et al., *Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure.* J Neurosurg Spine, 2007. **7**(2): p. 151-60.
11. Gerszten, P.C., et al., *Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution.* Spine (Phila Pa 1976), 2007. **32**(2): p. 193-9.
12. Ryu, S., et al., *Radiosurgical decompression of metastatic epidural compression.* Cancer, 2010. **116**(9): p. 2250-7.
13. Ryu, S., et al., *Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery.* Cancer, 2007. **109**(3): p. 628-36.
14. Yamada, Y., et al., *High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions.* Int J Radiat Oncol Biol Phys, 2008. **71**(2): p. 484-90.
15. Fourney, D.R., et al., *Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group.* J Clin Oncol, 2011. **29**(22): p. 3072-7.
16. Jensen, M.P., et al., *Comparative reliability and validity of chronic pain intensity measures.* Pain, 1999. **83**(2): p. 157-62.
17. Cella, D.F., et al., *The Functional Assessment of Cancer Therapy scale: development and validation of the general measure.* J Clin Oncol, 1993. **11**(3): p. 570-9.

13.0 APPENDICES

13.1 Appendix A – Eligibility Checklist

Inclusion Criteria

Must be answered **YES** for eligibility

1. Does the patient have pathologically proven malignancy?

   Yes / No

2. Does the patient have demonstrated metastatic epidural cord compression on diagnostic imaging?

   Yes / No

3. Has the patient been evaluated by neurosurgery or orthopedic surgery and is not proceeding?

   Yes / No

4. Has the patient had an appropriate pre-treatment work-up, including complete history, physical examination and neurologic evaluation?

   Yes / No

5. Does the patient have ECOG Performance Status 0-2?

   Yes / No

6. Is the patient at least 18 years old?

   Yes / No

7. Is either of the following true?:
   - The patient is not a woman of childbearing potential.
   - The patient has undergone negative serum or urine pregnancy test within 72 hours prior to the start of study therapy, agrees to utilize an adequate method of contraception throughout treatment and for at least 4 weeks after study therapy is completed, and has been advised of the importance of avoiding pregnancy during trial participation and the potential risks of an unintentional pregnancy.

   Yes / No

8. Has the patient signed study-specific informed consent?

   Yes / No

Exclusion Criteria

Must be answered **NO** for eligibility

1. Has the patient had prior radiotherapy to the area in question which would exceed published constraints if enrolled?

   Yes / No

2. Does the patient have spinal instability as indicated by imaging or physical exam?

   Yes / No

3. Does the patient have a radiosensitive histology including myeloma or lymphoma?

   Yes / No

4. Is the patient pregnant or breastfeeding?

   Yes / No

13.2 Appendix B – Common Toxicity Criteria

NCI CTCAE Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version 4.0

13.3 Appendix C – ECOG Performance Status

Performance Status	Definition
0	No symptoms; normal activity level
1	Symptomatic, but able to carry out normal daily activities
2	Symptomatic; in bed less than half of the day; needs some assistance with daily activities
3	Symptomatic; in bed more than half of the day
4	Bedridden

13.4 Appendix D – Neurologic and Functional Assessment

Neurologic Assessment (adapted from RTOG 0631, Appendix IV)

Symptoms:

Level	Tenderness	Radiculopathy
Cervical Spine		
Thoracic Spine		
Lumbar Spine		
Sacrum		

Strength (MRC grade):

Arm	Level	L	R	Leg	Level	L	R
Deltoid	C5/6			Iliopsoas			
Bicep	C5/6			Quadriceps			
Tricep	C6/7/8			Hamstrings			
Digits	C7/8/T1			Ant Tibilalis			
Interossei	C8/T1			Gastroc			

Sensation:

	Arm		Trunk		Leg	
	L	R	L	R	L	R
Normal						
Decreased						

Urinary Incontinence:

Present: _____ Absent: _____

Sphincter Tone:

Normal: _____ Decreased: _____ Absent: _____

Functional Assessment ((adapted from ICORG phase III trial, ASTRO 2014)

Mobility Score	
I	Ambulatory without aid
II	Ambulatory with aid
III	Not Ambulatory
IV	Paraplegia