J12133: Phase II Study of Post-Operative Stereotactic Radiosurgery for Solid Tumor Spine Metastases
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Research Site: The Johns Hopkins University School of Medicine

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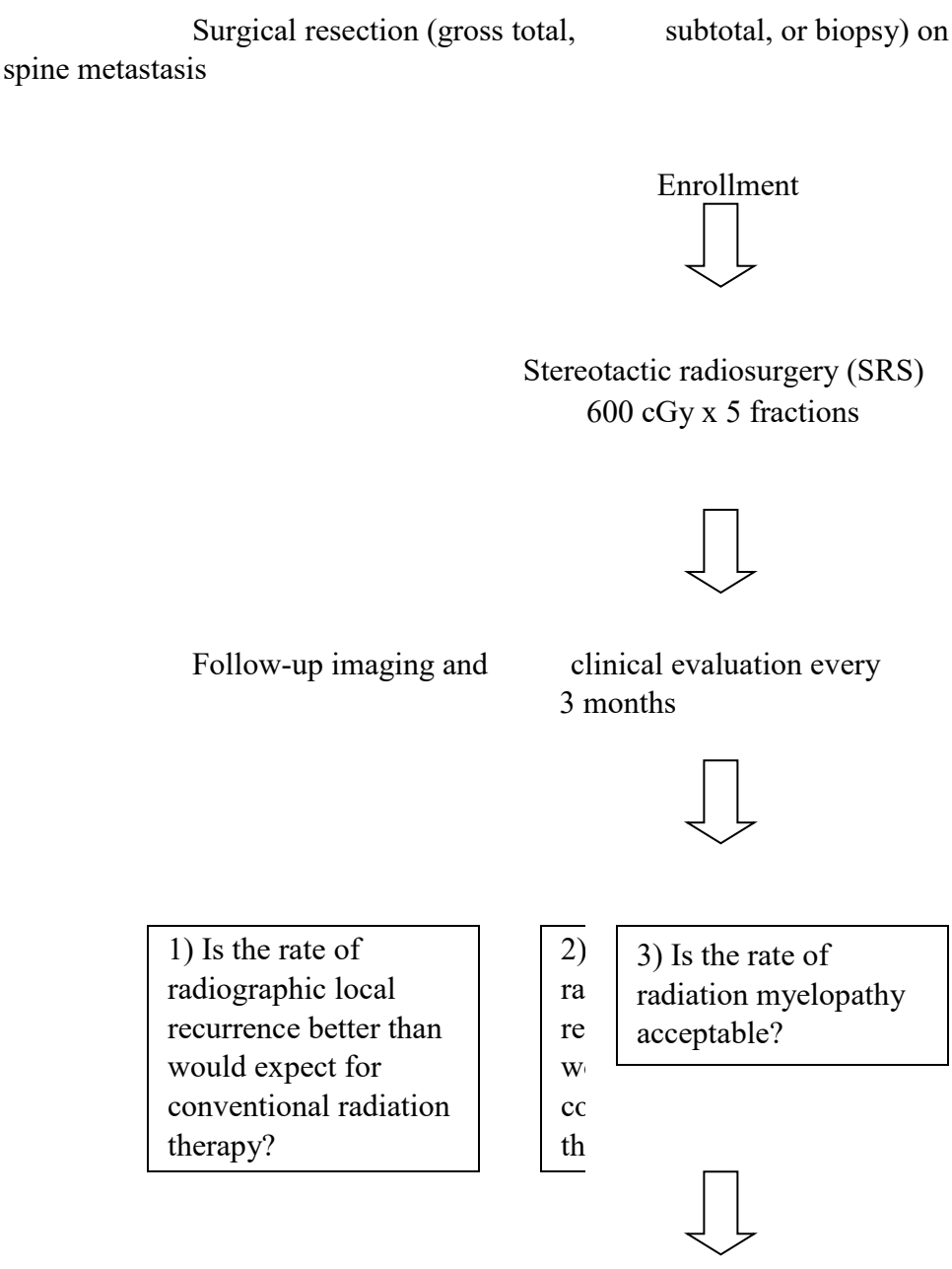
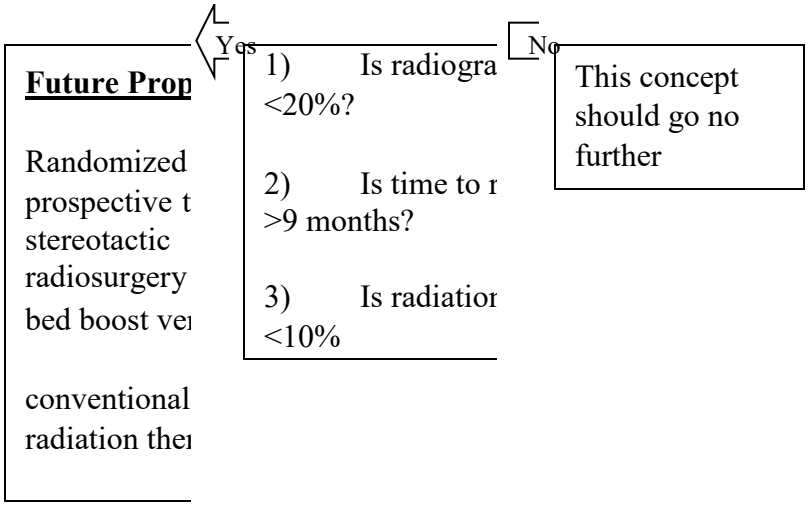
SCHEMA


Surgical resection (gross total, subtotal, or biopsy) on spine metastasis
Enrollment
Stereotactic radiosurgery (SRS)
600 cGy x 5 fractions
Follow-up imaging and clinical evaluation every 3 months
1) Is the rate of radiographic local recurrence better than would expect for conventional radiation therapy?
2) ra re w cc th
3) Is the rate of radiation myelopathy acceptable?



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1. OBJECTIVES

1.1 Primary Objective

To estimate the rate of radiographic local recurrence at 12 months in patients treated with a post-operative stereotactic radiosurgery boost for resected spine metastases.

1.2 Secondary Objectives

1.2.1 To estimate the time to radiographic local recurrence in patients treated with a post-operative stereotactic radiosurgery boost for resected spine metastases

1.2.2 To estimate the rate of re-treatment at 12 months in patients treated with a post-operative stereotactic radiosurgery boost for resected spine metastases

1.2.3 To estimate the rate of symptomatic local recurrence at 12 months in patients treated with a post-operative stereotactic radiosurgery boost for resected spine metastases

1.2.4 To estimate the rate of radiation myelopathy in patients treated with a post-operative stereotactic radiosurgery boost for resected spine metastases

1.2.5 To estimate the rate of wound dehiscence in patients treated with a postoperative stereotactic radiosurgery boost for resected spine metastases

1.2.6 To estimate the time to return to chemotherapy in patients treated with a post-operative stereotactic radiosurgery boost for resected spine metastases

1.2.7 To evaluate whether symptomatic local recurrence rates vary with tumor histology in patients treated with a post-operative stereotactic radiosurgery boost for resected spine metastases

2. BACKGROUND

2.1 Study Disease and Rationale

Approximately 40% of cancer patients are diagnosed with spine metastases at some point during their disease course (1) and up to 90% of terminal cancer patients have evidence of metastatic spinal disease on post-mortem studies (2-6). Management of spine metastases varies depending on the individual patient circumstances, but may include systemic therapy alone or radiation therapy. In patients with spinal instability, spinal cord compression, or neurologic deficits as a result of their spine disease, the standard of

care is direct decompression and/or stabilization followed by radiation therapy based on a large randomized study which revealed significantly higher rates of ambulation in patients undergoing surgical resection followed by radiation therapy versus radiation therapy alone (7).

Rates of local recurrence following surgical resection alone are high (Gilbert, Black, Greenberg, Rodriguez, Sorensen), likely at least in part as a result of difficulty attaining a widely negative surgical margin, especially in the epidural space. As such, radiation therapy is typically offered following surgical resection of a metastatic spine lesion in order to decrease the risk of local recurrence and development of neurologic deficits or cord compression. Historically most patients have been treated with conventional radiation therapy which generally involves 2-3 weeks of daily radiation treatment to both the involved vertebral levels as well as a vertebral level above and below. However, recurrence rates following conventional radiation therapy to the spine are high and patients frequently require retreatment for progressive or recurrent symptomatic disease (Klekamp and Samii, Chow E, Sze WM, Wu JS).

More recently, a 1-5 day course of stereotactic radiosurgery has been utilized as a method of delivering a higher biological equivalent dose and hopefully reducing local recurrence rates particularly in patients with oligometastatic disease, radioresistant primaries, recurrence after prior radiation therapy, high risk of epidural disease, or who have social or clinical need for shortened treatment duration. The safety and efficacy of SRS in patients with intact vertebral disease has been well established and is currently being compared to conventional radiation therapy in the context of a randomized controlled trial (RTOG 0631). Data suggests that in spite of the smaller field size with SRS, rates of marginal failure are low and local control rates are high (Ahmed IJROBP 2011; Gerszten, Jin, Ryu, Chang, Ryu). Although frequently performed in standard clinical practice, only 3 small retrospective studies have been published to date exploring the efficacy of SRS in post-operative patients with resected spine metastases (Rock, Moulding, Gerszten), and the role and benefit of SRS in this setting remains uncertain.

As systemic therapies improve and survival times increase for many cancers, it is likely that the incidence and prevalence of spinal metastases will increase as well, and improving management of spine metastases will be critical in minimizing pain, improving neurologic function, and potentially improving survival. The purpose of the study is to prospectively examine the efficacy of post-operative SRS boost in patients who have undergone surgical resection of metastatic spine disease.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥12 years

3.1.2 Histologically proven solid tumor malignancy with metastasis to the spine. Diagnosis may be acquired from needle biopsy, cytology, surgical biopsy or resection.

3.1.3 Radiographic evidence of spinal metastasis is required and may be obtained from radionuclide bone scans, computed tomography imaging, and magnetic resonance imaging. Other studies may be used with principal investigator approval, but plain radiograph (X-ray) alone is not sufficient.

3.1.4 The patient must have undergone surgical resection (gross total, subtotal, or biopsy) of the spinal lesion(s) no more than 16 weeks prior to SRS treatment.

3.1.5 Treating physician must deem that SRS is appropriate treatment for the metastatic spinal lesion(s).

3.1.6 Each SRS target must be the equivalent of ≤3 vertebral levels

3.1.7 The patient must have a Karnofsky Performance Score of 40 or greater (Appendix F).

3.1.8 If a woman is of child-bearing potential, a negative urine or serum pregnancy test must be demonstrated prior to treatment. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for up to 12 weeks following the study. Should a woman become pregnant or suspect she is pregnant while participating in this study she should inform her treating physician immediately.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Prior radiation or radiosurgery to the involved level of the spine

3.2.2 Spine disease from leukemia, lymphoma or myeloma

3.2.3 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements will be excluded.

3.2.4 Pregnant women are excluded. We recommend that women of child-bearing potential use an acceptable method of birth control to avoid pregnancy for 6

months following stereotactic radiosurgery and that male subjects use effective contraception for the same period.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

Patients will be accrued from Johns Hopkins Medical Institutes in Baltimore, MD. Contact information for the Principal Investigator is listed on the cover page.

To register the patient, the following documents must be completed and faxed to 443-2878354 or emailed the Study Coordinator.

- Copy pathology report
- Source documentation verifying eligibility
- Eligibility checklist
- Signed patient consent form
- HIPAA authorization form

If the patient is deemed eligible for the study, the Study Coordinator will register the patient and assign a study number.

5. TREATMENT PLAN

5.1 Treatment Planning

5.1.1 Simulation

All patients will be immobilized in a reproducible radiosurgery setup as deemed most appropriate by treating physician and clinical team. Patients will undergo CT simulation preferably both with and without intravenous contrast. If there is a contraindication to CT contrast it is ok to withhold it at the discretion of the treating physician. In addition, unless there is a contraindication to MRI they will undergo MRI simulation including T1 with gadolinium, T2 and STIR axial and saggital sequences. For precise delineation of the spinal cord, patients should undergo CT myelogram (optional) unless the spinal cord is adequately visualized on simulation MRI.

Scans should include at least 1 vertebral level above and below the involved levels.

5.1.2 Image Fusion

Following completion of simulation scans, the following datasets will be fused using the treatment planning software: 1) CT simulation; 2) CT myelogram (if performed); 3) pre-operative diagnostic scan; 4) MRI simulation. The exact sequences of these scans to fuse will be at the discretion of the treating radiation oncologist and neurosurgeon. If a patient is unable to undergo one of these scans he may remain on the protocol at the discretion of both the treating physician and principal investigator.

5.1.3 Tumor and Object At Risk (OAR) Delineation

Tumor and OARs will be delineated and approved by both the treating radiation oncologist and treating neurosurgeon.

5.1.3.1 Gross Tumor Volume (GTV)

GTV will defined as the residual disease as visualized on post-operative imaging.

5.1.3.2 Clinical Target Volume (CTV)

CTV will account for the GTV, tumor bed, and other sites of potential microscopic disease spread at the discretion of the treating physicians. The CTV should include areas of disease on pre-operative imaging as well as surgical findings as documented in operative notes and in personal communications with the surgeon. Surgical incision does not need to be included in the treatment volume except in unique situations where it is believed to be a region at high risk of recurrence.

5.1.3.3 Planning Target Volume (PTV)

PTV will include the CTV plus approximately 1.5-2 mm geometric expansion. PTV should be reduced as necessary so that the PTV does not extend into the cord contour.

5.1.3.4 Object at risk (OAR)

Adjacent OARs will be contoured on the simulation films. The maximal dose constraints are as follows:

Spinal cord (as defined on CT myelogram plus 2 mm). Should be delineated at least 1 vertebral body above and below PTV: 25 Gy to 0.1 cc

Cauda equina (defined as thecal sac on CT myelogram without margin). Should be delineated at least 1 vertebral body above and below PTV: 25 Gy to 0.1 cc

Esophagus: 32.5 Gy

Heart/pericardium: 35 Gy

Great vessels: 55 Gy

Trachea: 32.5 Gy

Skin: 40 Gy

Kidney: According to current Johns Hopkins Hospital standard SBRT practices

5.1.4 Radiation Prescription and Dosimetry

Patients will be treated to a total dose of 30 Gy with a once daily fractionation schedule of 6 Gy per fraction, administered Monday through Friday. Treatment may begin on any weekday with break for weekend, as long as the patient receives at least 2 fractions the first week. Radiation treatment planning will be performed by a specialized dosimetrist or physicist. Goal PTV coverage is >90% receiving >90% of prescription dose but coverage should be compromised as necessary to meet normal tissue constraints as outlined above and will not be considered a protocol deviation. Final plan approval and spinal cord dose is at the discretion of the treating physician and final prescription dose may be reduced to meet spine cord constraints if deemed necessary by the treating physician (for example, in cases of epidural disease or disease abutting the spine cord).

5.1.5 Equipment

Patients will be treated using a megavoltage linear accelerator with nominal beam energy of 6 MV.

5.1.6 Beam Verification

Either on-line cone beam CT guidance or orthogonal imaging will be used according to the standard Johns Hopkins radiosurgery protocol for precise patient setup. Images will be reviewed and approved by a physician prior to initiation of treatment.

5.1.7 Therapy Interruption

For radiation therapy interruptions of up to and including 5 days, irradiation should be completed to the full prescribed dose. On the last day, the total number of fractions and the reasons for interrupting therapy must be documented

If radiation therapy interruption goes beyond 5 days, the patient will be removed from the protocol treatment. Resumption and completion of treatment will then be at the discretion of the radiation oncologist in consultation with the principal investigator. All patients who initiate protocol treatment will be followed per the study calendar.

5.1.8 Risks of Radiation

Short term toxicities of radiation therapy include fatigue, nausea, vomiting, diarrhea, hair loss in treated area, erythema or irritation of the skin, dry skin, difficulties with wound healing, difficulty or pain with swallowing, worsening or new neurologic deficits, injury to nerves or spinal cord causing disability and pain, weakness of limbs, bowel and bladder dysfunction, decrease in blood cell counts, edema of cord requiring steroids, damage to the baby if patient is or becomes pregnant, decreased sperm count, death.

Long term toxicities include damage to spinal cord resulting in paralysis or death, damage to other normal structures such as kidney, lung, heart, liver, bowel, skin, esophagus, weakening of bone with increased risk of fracture, growth abnormalities of bones, muscles or other organs, second tumor or cancer caused by radiation.

5.2 Follow Up

Patients will be followed until the time of data analysis for the study. At two years following completion of post-operative stereotactic radiosurgery, follow-up imaging will be performed only at the discretion of the treating physician. It is preferred that follow-up imaging and evaluation be performed at Johns Hopkins, but they may also be performed at outside facilities as necessary for insurance, scheduling, or other reasons. If a patient is unable to be seen at Johns Hopkins for follow-up we will collect patient reported toxicity via telephone.

Follow-up imaging should include CT and/or MRI followed by CT myelogram (optional) if the results of initial imaging studies are inconclusive and the patient has symptomatic evidence of progression.

Follow-up evaluations will include a complete neurological exam and evaluation of the surgical wound, neurologic evaluation by the ASIA Impairment Scale (Appendix A), and pain evaluation by the 10 point visual analog scale (Appendix B) and MDACC brief pain inventory short form (Appendix C).

5.3 Toxicity

Toxicity will be recorded according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4. Early stopping will be considered for grade 4 or greater spinal cord toxicity according to this scale that is attributable to the study intervention. The criteria are available online at the Cancer Therapy Evaluation Program website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Toxicity will also be monitored according to the RTOG/EORTC acute (Appendix D) and late (Appendix E) common toxicity assessments for CNS and spinal cord. Consideration for early stopping will be considered for grade 4 or greater spinal cord toxicity according to this scale attributable to study intervention.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, radiosurgery will be administered for a total of 5 fractions or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed applies:

- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

The reason for study removal and the date the patient was removed must be documented in the Case Report Form. If a participant withdraws from the study, they will be followed for survival data.

6. CORRELATIVE/SPECIAL STUDIES

Not applicable.

7. STUDY CALENDAR

Every effort should be made to adhere to the protocol timeline as closely as possible, but if studies are delayed or missed as a result of unavoidable conflicts such as hospitalization at an outside facility, deteriorating of patient status, or other adversity precluding presentation for evaluation, it will not be considered a protocol deviation.

	Pre-Study	RT	Follow-up Post RT*								
			Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Q 6 Months[9]
Surgical resection of spine lesion[1]	X										
CT Myelogram (optional)	X										
Radiographic evidence of spine mets	X[10]										
Simulation	X[3]										
Radiosurgery		X									
Demographics	X										
Medical history[4] & Physical Exam	X		X	X	X	X	X	X	X	X	
Vital signs and Weight	X		X	X	X	X	X	X	X	X	
B-HCG[11]	X[2]										
CBC w/Diff	X		X	X							
Performance Status	X	X	X	X	X	X	X	X	X	X	
ASIA Impairment Scale	X[2]	X	X	X	X	X	X	X	X	X	
Brief Pain Inventory & 10 Point Visual Analog Scale	X[2]	X	X	X	X	X	X	X	X	X	
NCI Common Toxicity Criteria	X[2]	X	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	
RTOG Acute/Late Morbidity Criteria[5]	X[2]	X	X	X	X	X	X	X	X	X	
CT Scan[6] or MRI[7]			X	X	X	X	X	X	X	X	X

[1]Surgical resection includes gross total resection, subtotal resection, or biopsy. Margin status (negative, microscopically positive, gross disease) should be recorded. Margin status should be based on the pathology report if possible, but when not recorded on pathology report may be based on the operative note, post-operative imaging and/or personal communications between the treating physician and surgeon

[2]Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy.

[3]CT simulation is required for radiation treatment planning. CT simulation must be conducted within 8 weeks prior to protocol therapy. MRI simulation for treatment planning is at the discretion of the treating physician.

[4]Medical history should be a complete history at pre-study evaluation, but later histories will be interval histories only.
[5]Use RTOG Acute Toxicity Criteria during RT and for first 6 months following completion of RT. Use RTOG Late Toxicity Criteria at baseline and at scheduled intervals 6 months following completion of RT.
[6]CT scan may be performed with or without contrast
[7]Imaging which is delayed or missed as a result of the deterioration of the patient's clinical condition or other adversity will not be considered a protocol violation.
[8]If a patient is unable to be seen for a follow-up consult, we will assess the patient's condition via telephone.
[9]Patients will be followed until the time of data analysis for the study. At two years post radiosurgery, follow-up imaging will be performed only at the discretion of the treating physicians.
[10]Section 3.1.3
[11]Pregnancy test is required for women who are of child-bearing potential
*Follow-up visits may be performed within + or – 1 month from the scheduled visit date.

8. MEASUREMENT OF SYMPTOMATIC PROGRESSION

A patient will be considered to have symptomatic progression if: 1) there is radiographic evidence of progression on CT, MRI and/or CT myelogram based on direct comparisons by at least 2 members of the team of the most recently obtained radiographic images compared to the immediate pretreatment images AND 2) progressive symptoms defined as worsening neurologic function attributable to tumor growth at the level treated according to the ASIA Impairment Scale OR worsening pain attributable to tumor growth at the treated level according to the MDACC brief pain inventory (short form) defined as a *new* score ≥5 at the treated level of spine

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 Study Design

This is a phase II trial evaluating the rate radiographic local recurrence following post-operative stereotactic radiosurgery boost in patients with metastatic solid malignancies with spine metastases status post resection.

9.1.2 Endpoints

9.1.2.1 Primary Endpoint

Radiographic local recurrence at 12 months in each patient.
Radiographic local recurrence (LR) will be defined as evidence of progressive disease on CT and/or MRI in the treatment volume or at the margin of the treatment field when compared to imaging studies prior to the post-operative radiosurgical boost. The determination of local progression will be made by at least 1 radiation oncologist and 1 neurosurgeon and confirmed by a neuro-radiologist and the Principal Investigator. If equivocal, the lesion may be followed with serial short interval scans for further clarification. If the equivocal lesion develops into local recurrence on serial scans, the timing of local recurrence will be backdated to the date of the first suspicious CT or MRI.

9.1.2.2 Secondary Endpoints

9.1.2.2.1 Time to radiographic local recurrence in each patient

9.1.2.2.2 Re-treatment at 12 months in each patient
Retreatment is defined as either radiosurgery, conventional radiation therapy or surgical intervention to the area that was

treated because of tumor progression in that region as defined by imaging studies according to the primary objective

9.1.2.2.3 Symptomatic local recurrence at 12 months in each patient
Symptomatic local recurrence requires 2 of the following:
1) EITHER:
NEW pain in treated region of ≥5 on the MD Anderson Cancer Center brief pain inventory OR:
Worse performance on ASIA Impairment Scale

AND:
2) Evidence of local recurrence on imaging as defined in the primary objective

9.1.2.2.4 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 and RTOG/EORTC acute and late common toxicity assessments for CNS and spinal cord for each patients. Radiation myelopathy is defined as grade 4 or greater spinal cord toxicity according to this scale.

9.1.2.2.5 Examination of wound at each follow-up visit for each patient. Wound dehiscence is defined as a re-opening of the surgical wound which is independent from wound infection.

9.1.2.2.6 Time to return to chemotherapy in each patient measured from first day of radiosurgery treatment

9.1.2.2.7 Tumor histology in each patient

9.2 Sample Size/Accrual Rate

9.2.1 Sample Size

A total of 35 patients will be enrolled in the protocol. Assuming a 60% radiographic local control rate at 12 months with conventional radiation therapy (Rades 2009), our trial will need a total of 35 patients to yield 80% power detecting 20% absolute improvement (LC=80%) at an alpha level of 0.05 (one-sided) to be statistically significant.

9.2.2 Accrual

We anticipate enrollment of approximately 1-2 patients per month to the protocol with accrual completed in approximately 24 months.

9.2.2.4 **Stratification Factors**

There will be no stratification factors upon initial enrollment in the protocol.

9.3 Statistical Analysis plan

9.3.1 Primary:

The proportion of patients who were absence of local recurrence (local control) at 12 months after initial SRS will be estimated along with 90% confidence interval. The local recurrence is defined in section 9.1.2.1.

9.3.2 Secondary:

Time to radiographic local recurrence will be calculated from the date of initial SRS to the date of LR was documented. Probability of time to LR and median time to LR will be estimated using Kaplan-Meier method.

A proportion of patient being retreated during first 12 months since initial SRS will be estimated along with 95% confidence interval.

The symptomatic local recurrence rate at 12 months will be estimated along with 95% confidence interval using binomial distribution.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and RTOG/EORTC acute and late common toxicity assessments for CNS and spinal cord will be used for scoring toxicity and adverse events. The proportion of patients who experience grade 3 or above toxicities will be estimated, along with 95% confidence intervals by each type of toxicity. Observed sever adverse event associated with SRS including radiation myelopathy will be summarized using descriptive statistics.

Time to return to chemotherapy will be calculated from the date of initial SRS to the starting date of chemotherapy. The chemotherapy date is censored if patient has not had chemotherapy at time the study database is closed for final analysis. Probability of time to return to chemotherapy will be estimated using Kaplan-Meier method.

Patient's tumor histology and wound healing will be summarized using descriptive statistics.

10. ADVERSE EVENTS AND RECORDING

10.1 Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following an exposure to a treatment, whether or not considered causally related to the treatment. An undesirable medical condition may be symptoms (headache, nausea), signs (tachycardia, enlarged liver), or abnormal results of an investigation (MRI, laboratory finding). In clinical trials,

from the time of signing an informed consent, an AE may include an undesirable medical condition, occurring at any time, even if no trial treatment has been administered.

10.2 Radiation Related Adverse Events

All radiation related adverse events will be recorded on the local toxicity case report forms.

11. SERIOUS ADVERSE EVENTS (SAE) AND REPORTING

11.1 Serious Adverse Event

11.1.1 Definition of Serious Adverse Event

A serious adverse event is an AE occurring at any point during a clinical trial that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Is a congenital abnormality or birth defect.
- Unexpected event that cause harm or place person at a greater risk of harm than was previously known or recognized, and which was possibly related to the research. Unexpected means that the event was not described in the consent form or the event exceeded the expected severity.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

11.2 SAE Reporting Guidelines for Johns Hopkins Hospital

All SAE, with the exception of death, must be reported to the Johns Hopkins Hospital Institutional Review Board (JH-IRB) within 10 working days of the principal investigator learning of the event. Reporting for the death of a patient which was unexpected (i.e.: not related to a risk of participation that was listed in the protocol or the consent document, and was more likely than not to be caused by the research procedure/intervention, must be reported to the JH-IRB within 3 working days of when the principal investigator receives the report of the death. Reporting for death of a participant that was expected due to the nature of the patient's underlying disease or condition, or identified as caused by a possible risk of the study procedure/intervention as described in this protocol or consent form, must be reported

to the JH-IRB within 10 working days from the time the principal investigator learns of the event. If death occurs 30 days after the participant has stopped or completed their study treatment, the principal investigator does not have to report the death until the time of continuing review.

12. DATA AND SAFETY REPORTING/ REGULATORY CONSIDERATIONS

12.1 Data Quality Monitoring

In addition to the ongoing quality assurance evaluations for each individual at the time of treatment, there will be regular internal monitoring meetings between the principal investigator, a medical oncologist, and the study coordinator to assess the data quality. These meetings will occur annually and a monitoring report of the findings will be submitted to the Data Safety Monitoring Committee on an annual basis. Any protocol deviations or violations will be documented in the monitoring reports. The review will include: consent forms, eligibility criteria, protocol compliance, treatment administration, toxicity reports, response, regulatory compliance, case report forms (completeness as well as verifying that information coded on the case report forms are supported by source documents), and all other materials related to the trial. This is a Level I study under the SKCCC Data Monitoring Plan (date). The Clinical Research Office QA group will assume external auditing responsibilities by performing an audit at the end of the first year and then periodically thereafter depending on the rate of accrual and prior audit results. The Safety Monitoring Committee will review this trial for safety and data quality annually.

12.2 Data Safety Monitoring Plan

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/6/2012). The Clinical Research Office QA Group will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee.

The PI is responsible for monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study. The PI will also be responsible for maintaining the clinical protocol, reporting adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the continuing renewal report submitted to the IRB and to the trial monitoring review group.

12.3 Data Reporting

12.3.1 Method

Data will be collected on Case Report Forms (CRFs). These CRFs will be completed by the study coordinator. The CRFs for each subject will be kept in a separate research binder. Along with each completed CRF there will be corresponding source documentation filed for verification. The Principal Investigator, Research Study Nurse, and Study Coordinator will informally meet on a regular basis to make sure that the trial is progressing as mandated by the protocol. The CRO will audit this trial per their standards to ensure and verify that the protocol is be carried out according to specs as well as to verify that data included on subject CRFs are accurate. Exit reports generated as a result of these CRO audits will be forwarded to both the Safety Monitoring Committee as well as to the adjudicating IRB of record for review.

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Patient Name _____

Examiner Name _____ Date/Time of Exam _____

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ASIA American Spinal Injury Association

ISCOS

MOTOR

KEY MUSCLES (scoring on reverse side)

	R	L	
C5	☐	☐	Elbow flexors
C6	☐	☐	Wrist extensors
C7	☐	☐	Elbow extensors
C8	☐	☐	Finger flexors (distal phalanx of middle finger)
T1	☐	☐	Finger abductors (little finger)

UPPER LIMB TOTAL (MAXIMUM) ☐ + ☐ = ☐ (25) (25) (50)

Comments:

L2	☐	☐	Hip flexors
L3	☐	☐	Knee extensors
L4	☐	☐	Ankle dorsiflexors
L5	☐	☐	Long toe extensors
S1	☐	☐	Ankle plantar flexors

(VAC) Voluntary anal contraction (Yes/No) ☐

LOWER LIMB TOTAL (MAXIMUM) ☐ + ☐ = ☐ (25) (25) (50)

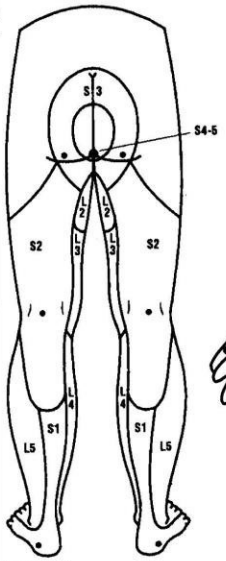
LIGHT TOUCH / PIN PRICK

	LIGHT TOUCH R	LIGHT TOUCH L	PIN PRICK R	PIN PRICK L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S4-5				
TOTALS (MAXIMUM)	☐ (56)	☐ (56)	☐ + ☐ = ☐ (56)	☐ + ☐ = ☐ (56)

SENSORY

KEY SENSORY POINTS

0 = absent
1 = altered
2 = normal
NT = not testable



• Key Sensory Points

(DAP) Deep anal pressure (yes/No) ☐

PIN PRICK SCORE (max: 112) ☐

LIGHT TOUCH SCORE (max: 112) ☐

NEUROLOGICAL LEVEL *The most caudal segment with normal function*	SENSORY R ☐ L ☐ MOTOR R ☐ L ☐	**SINGLE NEUROLOGICAL LEVEL** ☐	**COMPLETE OR INCOMPLETE?** ☐ *Incomplete = Any sensory or motor function in S4-S5* **ASIA IMPAIRMENT SCALE (AIS)** ☐	*(In complete injuries only)* **ZONE OF PARTIAL PRESERVATION** *Most caudal level with any innervation*	SENSORY R ☐ L ☐ MOTOR R ☐ L ☐

REV 04/11

Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position.

5 = (normal) active movement, full ROM against gravity and full resistance in a muscle specific position expected from an otherwise unimpaired peson.

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present.

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50% of the range of motion).

ASIA Impairment (AIS) Scale

☐ **A = Complete.** No sensory or motor function is preserved in the sacral segments S4-S5.

☐ **B = Sensory Incomplete.** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5: or deep anal pressure (DAP)), AND no motor function is preserved more than three levels below the motor level on either side of the body.

☐ **C = Motor Incomplete.** Motor function is preserved below the neurological level**, and more than half of key muscle functions below the single neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0-2).

☐ **D = Motor Incomplete.** Motor function is preserved below the neurological level**, and <u>at least half</u> (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3.

☐ **E = Normal.** If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

**For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing <u>with</u> sparing of motor function more than three levels below the motor level for that side of the body. The Standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the ***motor level*** on each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the ***single neurological level*** is used.

Steps in Classification

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete. (i.e. absence or presence of sacral sparing)
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores =* **0** *AND deep anal pressure =* **No,** *then injury is COMPLETE. Otherwise, injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury <u>Complete?</u> If **YES,** AIS=A and can record ZPP (lowest dermatome or myotome on each side with some preservation)

NO ↓

Is injury motor <u>Incomplete?</u> If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

YES ↓

Are <u>at least</u> half of the key muscles below the single <u>neurological</u> level graded 3 or better?

NO ↓ AIS=C

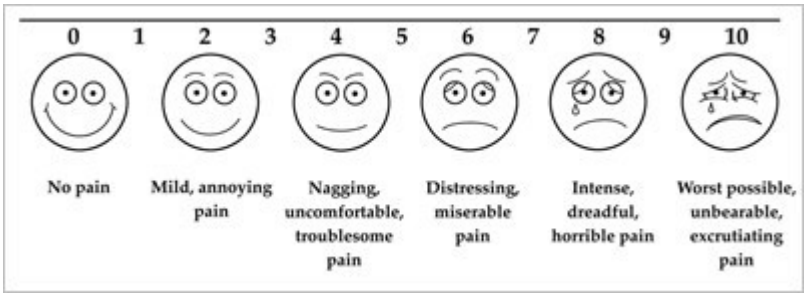
YES ↓ AIS=D

If sensation and motor function is normal in all segments, AIS=E

Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

APPENDIX B:

10 point Visual Analog Scale



APPENDIX C:

MDACC Brief Pain Inventory (Short Form)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

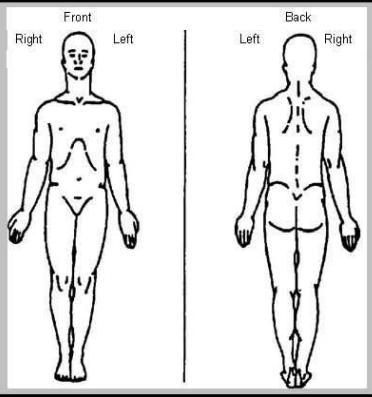
Name: _____ _____ _____

Last First Middle Initial

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 every-day kinds of pain today?

1. Yes 2. 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 circling the one 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 circling the one 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 circling the one 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 circling the one 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

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:___/____/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

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 circle the one 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. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

APPENDIX D:

RTOG Acute Morbidity Scoring Criteria

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	No change over baseline	Faint erythema, epilation, dry desquamation, or decreased sweating	Tender or bright erythema, patchy moist desquamation, moderate erythema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Eye	No change over baseline	Mild conjunctivitis with or without scleral injection, increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids and/or antibiotics, dry eye requiring artificial tears, iritis with photophobia	Severe keratitis with corneal ulceration, objective decrease in visual acuity or in visual fields, acute glaucoma, panopthalmitis	Loss of vision (unilateral or bilateral)
Ear	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged over baseline.	Moderate external otitis requiring topical medication, serous otitis media, hypoacusis on testing only	Severe external otitis with discharge or moist desquamation, symptomatic hypoacusis, tinnitus, not drug related	Deafness
CNS	No change over baseline	Fully functional status with minor neurologic findings, no medications needed	Neurologic findings present sufficient to require home care. Nursing care may be required. Medications including steroids and/or anti-seizure agents	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which included paralysis, coma, or seizures, despite medications. Hospitalization required
Hematologic WBC (x1000)	≥ 4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
Platelets (x 1000)	≥ 100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
Neutrophils	≥ 1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
Hematocrit (%)	≥ 32	28 - <32	<28	Packed cell transfusion required	N/A

APPENDIX E:

RTOG Late Radiation Morbidity Scoring Criteria

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	None	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss	Marked atrophy, gross telangioectasia	Ulceration	Death directly related to late radiation effect
Subcutaneous Tissue	None	Slight induration and loss of subcutaneous fat	Moderate fibrosis but asymptomatic. Slight field contracture. <10% linear reduction	Severe induration and loss of subcutaneous tissue. Field contracture >10% linear measurement	Necrosis	
Spinal Cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurologic findings at or below cord level treated	Mono-, para-, quadra-plegia	
Brain	None	Mild headache, slight lethargy	Moderate headache, great lethargy	Severe headaches, severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures, paralysis, coma	

Eye	None	Asymptomatic cataract, minor corneal ulceration of keratitis	Symptomatic cataract, moderate corneal ulceration, minor retinopathy or glaucoma	Severe keratitis, severe, retinopathy or detachment, severe glaucoma	Panopthalmitis, blindness	

APPENDIX F:

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.