

**Phase III Multicenter Randomized Study Comparing Local Tumor Control
After Post-Operative Single-Fraction or Hypofractionated Stereotactic
Radiosurgery in the Treatment of Spinal Metastases**

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Ilya Laufer M.D.	Neurosurgery
Co-Principal Investigator(s)/Department:	Yoshiya Yamada M.D. Mark Bilsky M.D. Eric Lis M.D.	Radiation Oncology Neurosurgery Radiology
Investigator(s)/Department:	Patrick Boland M.D. Zhigang Zhang Ph.D George Krol M.D. Sasan Karimi M.D. Sean McBride M.D. Adam Schmitt M.D. Daniel Higginson M.D.	Orthopedic Surgery Biostatistics Radiology Radiology Radiation Oncology Radiation Oncology Radiation Oncology
Consenting Professional(s)/Department:	Yoshiya Yamada M.D. Ilya Laufer M.D. Mark Bilsky M.D. Patrick Boland M.D. Adam Schmitt M.D. Daniel Higginson M.D.	Radiation Oncology Neurosurgery Neurosurgery Orthopedic Surgery Radiation Oncology Radiation Oncology

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Participating Institutions – If multicenter study coordinated by MSKCC:	PI's Name	Site's Role
Massachusetts General Hospital	John H. Shin M.D.	Data Collection
Johns Hopkins University	Daniel M. Sciubba M.D.	Data Collection
Stanford University	Scott Soltys M.D.	Data Collection

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA.....2

2.0 OBJECTIVES AND SCIENTIFIC AIMS4

3.0 BACKGROUND AND RATIONALE4

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION8

 4.1 Design.....8

 4.2 Intervention9

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS9

6.0 CRITERIA FOR SUBJECT ELIGIBILITY9

 6.1 Subject Inclusion Criteria.....9

 6.2 Subject Exclusion Criteria10

7.0 RECRUITMENT PLAN10

8.0 PRETREATMENT EVALUATION10

9.0 TREATMENT/INTERVENTION PLAN11

10.0 EVALUATION DURING TREATMENT/INTERVENTION11

11.0 TOXICITIES/SIDE EFFECTS13

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT15

13.0 CRITERIA FOR REMOVAL FROM STUDY15

14.0 BIostatISTICS16

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES17

 15.1 Research Participant Registration.....17

 15.2 Randomization18

16.0 DATA MANAGEMENT ISSUES19

 16.1 Quality Assurance22

 16.2 Data and Safety Monitoring23

17.0 PROTECTION OF HUMAN SUBJECTS25

 17.1 Privacy26

 17.2 Serious Adverse Event (SAE) Reporting26

 17.2.127

18.0 INFORMED CONSENT PROCEDURES28

19.0 REFERENCES30

20.0 APPENDICES33

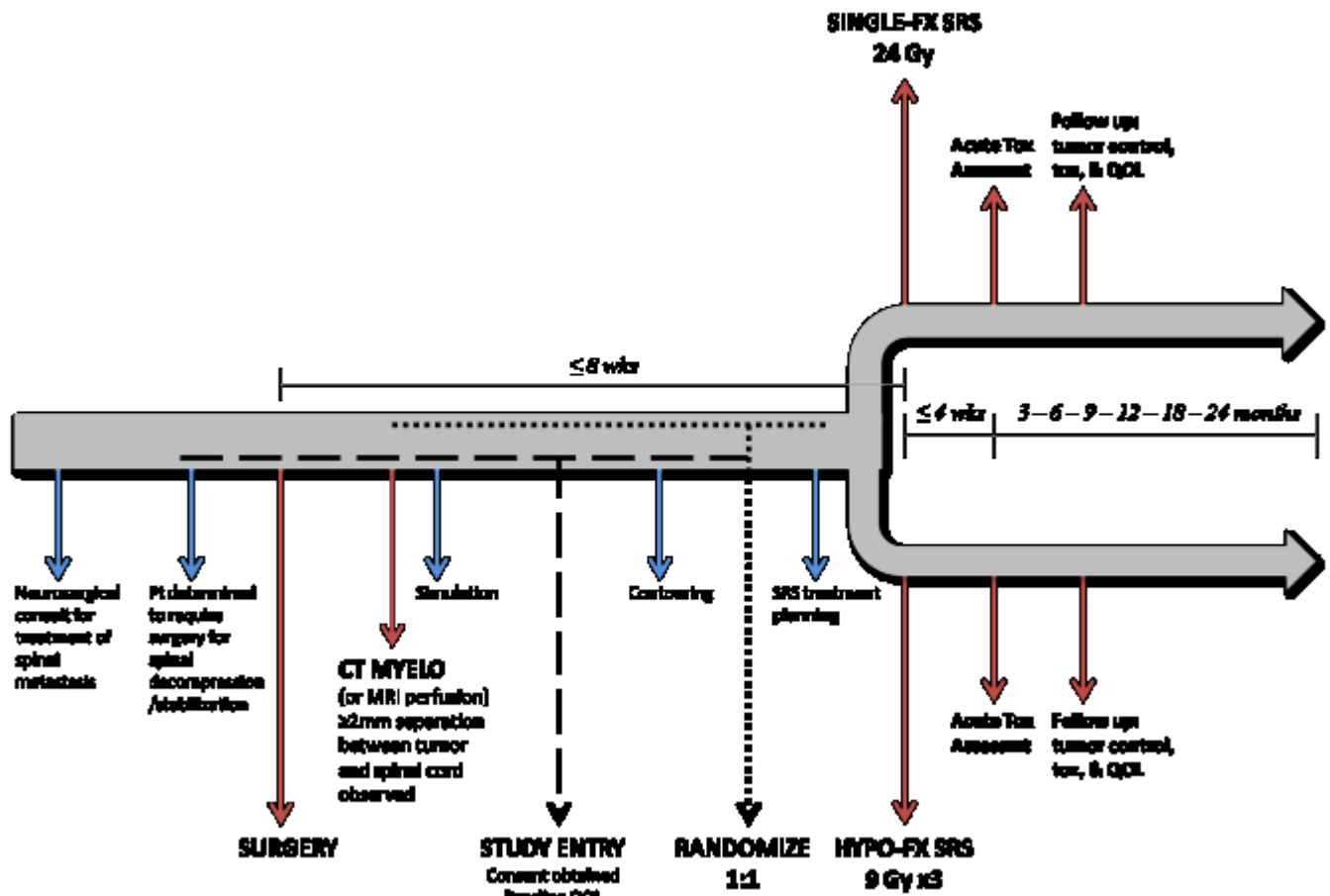
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Metastatic disease of the spine affects nearly 20% of patients with cancer and poses a growing problem as improved neo-adjuvant strategies allow longer life expectancy.

This is a Phase III multicenter clinical trial designed to prospectively evaluate the comparative effectiveness of single-fraction and hypofractionated stereotactic radiosurgery (SRS) in patients who underwent decompressive surgery for spinal metastases with a primary endpoint of local tumor control. Secondary objectives will evaluate complications and quality of life measures. Collaborating institutions include Massachusetts General Hospital (MGH), Johns Hopkins University (JHU), and Stanford University.

Eligible patients will have undergone spinal decompressive surgery for the treatment of high grade metastatic epidural spinal cord compression and demonstrate post-operative separation between tumor and the spinal cord on CT myelogram or MRI perfusion. This is a non-inferiority study in which patients will be randomized in a 1:1 ratio to undergo either single-fraction SRS (24 Gy) or high-dose hypofractionated SRS (27 Gy in 3 fractions) within 8 weeks of surgery. The treatment duration will be 1 to 7 days.

Study enrollment of 150 patients will be completed within two years. After randomization, patients will be followed up at 3, 6, 9, 12, 18, and 24 months (± 8 weeks) when possible or until death. The study duration will be up to four years. The primary endpoint will be local tumor control after SRS as monitored through imaging at follow up.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- The primary objective of this study is to evaluate the comparative effectiveness of single-fraction and high-dose hypofractionated SRS in achieving local tumor control for patients who underwent spinal decompressive surgery as treatment for metastatic epidural spinal cord compression tumors.

Secondary Objectives:

- To compare the risks and complication profiles of radiation-related toxicity between the two cohorts,
- To compare quality of life (QOL), as measured by the MD Anderson Symptom Inventory – Spine Tumor Module (MDASI), between the two cohorts and
- To compare pain control, as measured by the Brief Pain Inventory (BPI), between the two cohorts.

3.0 BACKGROUND AND RATIONALE

3.1 Metastatic spine tumors

The incidence of metastatic spine tumors is nearly 20% and has been increasing due to improvements in neo-adjuvant strategies. These allow for longer patient survival and thus increased incidence of progression to metastatic disease¹. The median survival for patients undergoing surgery for spinal metastatic tumors ranges from 7.0 – 16.5 months²⁻⁶. More specifically, the median survival varies depending on the histological type of primary cancer^{2,4}. However, with the development of superior systemic therapies which extend survival, these numbers are becoming outdated.

Diagnosis of spinal metastasis is made reliably based on clinical, radiographic and histologic grounds. Metastases to the skeletal system are the third most often involved system after the lungs and liver. Of this, nearly half are metastases of the spine. The majority of spinal metastases involve disease of the vertebral body with or without epidural compression. It is estimated that 5-10% of patients with spinal metastases will develop symptomatic spinal cord compression requiring surgical intervention⁷. The NOMS paradigm provides a widely-accepted guide to relevant considerations (Neurologic, Oncologic, Mechanical and Systemic) when determining the optimal combination of systemic, radiation and surgical therapies for individual patients with spinal metastases⁸. Yet despite advances in surgical and radiologic treatments, local recurrence of spinal metastasis remains a challenging problem and can lead to progression of spinal column instability, nerve/spinal cord compression and may require repeat surgery^{9,10}. Further study on improving the local recurrence of spinal metastases is warranted and has great clinical implications for the evaluation and counseling of patients.

3.2 Surgery for the treatment of high grade epidural spinal cord compression metastases

Surgical treatment of spinal metastases largely serves a palliative function. Clinical features of spinal metastases include any or all of the following: pain (local or radicular), sensory and motor deficits, and bowel/bladder dysfunction. The goals of surgical intervention include preservation or restoration of both neurologic function and spinal stability as well as improvement of pain control appropriate for the patient's burden of disease. Currently, surgical indications include spinal cord compression secondary to radioresistant and/or previously radiated spinal metastases or mechanical instability of the spinal column. After surgery, local tumor control is of paramount importance in order to maintain neurologic function, prevent hardware fracture and instability, and to maintain pain control.

A prospective multicenter trial that randomized patients with spinal cord compression secondary to solid metastatic tumors showed that patients who underwent surgery followed by radiation had superior outcomes compared to patients who only underwent radiation therapy without surgery. The surgical arm showed higher rate of ambulation recovery, preservation of ambulation and bowel/bladder continence as compared to the radiation arm¹¹. While the trial has several shortcomings, it provides fairly convincing evidence that surgery plays a beneficial role in patients with spinal cord compression secondary to solid tumors as compared to radiation treatment alone. This is further supported by the outcomes of numerous large retrospective case series.

Surgical intervention includes either posterior and/or anterior approach including laminectomy or corpectomy to various degrees and may involve instrumentation posteriorly (pedicle fixation, screw/rod system) and/or anteriorly (cage).

3.3 Post-operative SRS

Spinal metastases exhibit a range of sensitivity to radiation therapy. In patients with previous radiation to the surgical site, and/or with primary tumor histologies that respond poorly to conventionally fractionated radiation, spinal SRS provides safe and durable local control. The efficacy and safety of post-operative SRS in the treatment of spinal metastatic tumors was recently described¹². Single-fraction SRS and high-dose hypofractionated SRS both provide excellent tumor control (9% vs 4.1% estimated 1-year cumulative recurrence incidence) after spinal decompression surgery for high grade spinal cord compression. These data suggest that high-dose hypofractionated SRS may provide superior local tumor control compared to single-fraction SRS, however our retrospective study was not powered to detect this difference. The current trial is designed to evaluate whether single-fraction SRS provides comparable local control to high-dose hypofractionated SRS.

3.4 Radiobiology of Stereotactic Radiosurgery (SRS)

Radiation therapy is a well-established treatment for localized spinal metastases^{13,14}. The outcomes of treatment of spinal metastases using conventional external beam radiation therapy (cEBRT) delivered as a series of low-dose fractions have been fairly well documented¹⁵⁻¹⁸. Several prospective studies have shown that response to cEBRT may be predicted based on the primary tumor histology, leading to a dichotomization in characterizing tumor histologies as either radiosensitive or radioresistant^{14,15,19,20}. Hematologic malignancies were fairly uniformly considered radiosensitive, showing excellent local control rates after cEBRT. Breast and prostate were also reported to consistently respond to cEBRT. On the other hand, the majority of solid tumor metastases were classified as radioresistant to cEBRT.

The doses of cEBRT that can be delivered to the tumor are often limited by the risk of toxicity to surrounding organs since the beam is delivered to a broad field. On the other hand, image-guided stereotactic radiosurgery (SRS) allows the delivery of several high-dose fractions or a single high-dose of radiation with very high spatial precision thereby largely sparing surrounding organs from risk of exposure to high doses of irradiation²¹.

Radiation employs numerous pathways in order to kill tumor cells. The mechanisms of tumor response from single-fraction radiotherapy may differ from that of fractionated radiotherapy. Laboratory data show that single-fraction high-dose radiation employs tumor kill pathways that are not recruited at low-dose radiation fractions²². Radiation doses above 8Gy induce vascular endothelial apoptosis through activation of sphingomyelin-ceramide pathway and the extent of apoptosis increases as the radiation dose increases from 11 to 25 Gy²³. Furthermore, crypt stem cell clonogen apoptosis has been shown to require radiation doses that were on average 3.9 Gy higher than for endothelial apoptosis²⁴.

3.5 Single-fraction SRS

Single-fraction spine SRS provides durable and consistent local control in patients with spinal metastases¹³. The dose escalation study of single-fraction SRS treatment of spinal metastases that was carried out at MSKCC showed that 24 Gy dose resulted in 3-year recurrence risk of 2.4% which was significantly better than the 10% risk after lower doses^{21,25}. Furthermore, tumor control was independent of tumor volume and histology. MD Anderson reported similar tumor control along with improvement in the quality of life²⁶.

3.6 Hypofractionated SRS

Hypofractionated SRS was used to treat seventy-four spinal metastases, with actuarial one-year local control rate of 84%²⁷. The radiation was administered in five 6 Gy fractions or in three 9 Gy fractions, without a statistically significant difference in tumor control. Similar results were reported after five fractions to a total dose from 30 Gy to 35 Gy (1-year 80% and 2-year 73% actuarial local control). The experience in the use of hypofractionated SRS in the treatment of brain and lung tumors is more extensive and similarly indicates that hypofractionation provides a safe and effective treatment option²⁸.

3.7 SRS Toxicity Profile

Multiple studies reported low risk of toxicity after spinal SRS. The majority of events involved Grade 1 or 2 skin and esophageal toxicity²¹. To date, hypofractionated treatment of the spine has not been reported to result in Grade 3 or 4 neurologic toxicity. Single cases of Grade 3 vomiting, diarrhea, costochondritis and dysphagia were reported after hypofractionated treatment^{29,30}. To date, radiation literature describes nine cases of radiation myelopathy that have been attributed to single-fraction spinal radiation, confirming that this is an exceedingly rare consequence of spinal radiation³¹. Furthermore, in this institution no cases of radiation-induced myelopathy have been observed using cord point-maximum dose of 14Gy in patients without prior radiation history. A crude rate of Grade ≥ 3 esophageal toxicity of 6.8% was reported in our institution following single-fraction spine SRS³². Two Grade 4 acute esophageal toxicities, four Grade 4, and one Grade 5 late esophageal toxicities occurred. All of these events occurred in patients with either iatrogenic esophageal manipulation or with a history of radiation recall chemotherapy.

Some evidence suggests that administration of individual radiotherapy doses of 20 Gy or greater per fraction may lead to an increased risk of vertebral compression fracture³³. These findings remain limited as there are few studies that have compared single-fraction and hypofractionated SRS dosing schemes particularly in the post-operative period, thereby underscoring the clinical value of this prospective trial.

3.8 Quality of Life Measures: MDASI and BPI

As part of this study, we aim to assess a variety of symptoms experienced by cancer patients and to what degree these symptoms impede with daily living at baseline and at 3, 6, 9, 12, 18, and 24 months (± 8 weeks) after treatment during follow up care. In order to measure this, we will utilize the MD Anderson Symptom Inventory – Spine Tumor Module (MDASI) as an optional measure to evaluate each cohort of the study. MDASI has been validated as an instrument for use in clinical trials^{29,34,35} with Cronbach alpha reliability ranges from 0.82 to 0.94³⁴. This instrument (see Appendix A) contains 24 questions that ask patients to self-report about symptoms experienced in the last 24 hours on a scale of 0 (not present) to 10 (as bad as you can imagine). Thus, higher scores indicate more severe symptoms. Scoring of symptom severity and scoring of symptom interference will be performed as indicated in the Outcome Measure section of the MDASI User Guide (see Appendix B).

A second optional tool we will employ is the Brief Pain Inventory (BPI) to assess both the severity of pain experienced by participants and to what degree pain invades their ability to carry out daily functions at baseline and at 3, 6, 9, 12, 18, and 24 months (± 8 weeks) after treatment during follow up care. The BPI has been validated as an instrument for use in clinical trials^{29,36} with Cronbach alpha reliability ranges from 0.77 to 0.91³⁷. Patients are asked a total of 9 questions regarding their pain during in the last 24 hours (see Appendix C). Response formats include: Yes/No, scale of 0 (no pain) to 10 (pain as bad as you can imagine), illustrated region(s) of pain, pain relief as measured by 0% (no relief) - 100% (complete relief), pain interference of daily functions scale of 0 (does not interfere) to 10 (completely interferes). Higher score responses indicate more severe pain. No scoring algorithm exists, however the arithmetic mean of the four most severe items can be used as a measure of pain severity as indicated in the BPI User Guide (see Appendix D). The

arithmetic mean of the seven interference items (of question 9) can be used as a measure of pain interference³⁷.

3.9 Benefit

Spinal radiosurgery has been shown to provide durable and effective tumor control with very low risk of significant toxicity. Retrospective review of post-operative SRS suggests that there may be a difference in the tumor control provided by hypofractionated and single-fraction SRS¹². Hypofractionated SRS requires more patient visits and may be associated with higher cost. However, higher dose per fraction treatment (ie. single-fraction vs hypofractionated) may be associated with a higher risk of vertebral body fractures and generally requires increased complexity of dose planning. Clear delineation of the differences in tumor control and toxicity profile will facilitate the best treatment selection in the future. The current study is designed to prospectively study the safety and efficacy of post-operative SRS administered as either single-fraction or hypofractionated dose and to determine its impact on the quality of life.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a therapeutic Phase III prospective randomized non-inferiority study investigating the efficacy and safety of post-operative single-fraction or high-dose hypofractionated SRS. Diagnostic and eligibility decisions for patients entering the study will involve the RSA and ultimately will be made by the consenting professionals.

Eligible patients will have undergone surgery for spinal decompression and stabilization in order to treat spinal metastases and demonstrate adequate separation between tumor and the spinal cord on post-operative CT myelogram or MRI perfusion. Contrast used for the CT myelogram will not affect renal function and will be performed regardless of the participant's renal function. The CT myelogram or MRI perfusion will be performed at all participating sites. CT myelogram will be used for treatment planning, since spinal instrumentation generates artifact in MR imaging which may complicate spinal cord contouring. For instances in which the CT myelogram cannot be tolerated by the patient, MRI with perfusion will be an acceptable alternative for treatment planning. However, post-operative MR imaging provides adequate resolution in order to reliably diagnose tumor recurrence and will be used to monitor patients for recurrence, unless patients are unable to undergo MR imaging.

Patients who are candidates for either single-fraction or high-dose hypofractionated SRS will be recruited into the study and randomized in a 1:1 fashion to one of the two treatment arms. An Acute Toxicity Assessment (see Appendix E) will be performed via phone or clinic visit within 4 weeks (\pm 10 days) after the completion of SRS. Patients will have the option to complete the MD Anderson Symptom Inventory – Spine Tumor Module (MDASI) and the Brief Pain Inventory (BPI) at the time of recruitment and at 3, 6, 9, 12, 18 and 24 months (\pm 8 weeks) after their treatment during follow-up care. At these same time points, the study investigators will complete the Spine Clinic Assessment form (see Appendix F). Follow-up MRI imaging will also be obtained at the same time points, including axial and sagittal T1, T2, STIR and gadolinium-enhanced T1 sequences. For those patients that are not candidates for

MRI, CT imaging will be performed. Patients will be monitored for development of radiation- and surgery-related toxicity or complications. Imaging will be reviewed for evidence of local tumor progression.

4.2 Intervention

In this study, patients who fulfill the diagnostic criteria of high grade metastatic spinal cord compression and who have undergone decompression surgery and post-operatively demonstrate separation between tumor and the spinal cord as stated above will be eligible for study entry. Patients will require SRS based on the radioresistant nature of their primary histology and/or previous radiation history. Eligible patients will be recruited and following informed consent will be randomized to undergo single-fraction (24Gy) or hypofractionated (3 fractions of 9Gy, total dose of 27Gy) SRS within eight weeks of having undergone spinal decompression surgery. The contouring and dosimetry will be done using standard institutional practice and dose constraints. If more than one lesion will require treatment, the patient will be evaluated for inclusion in the protocol. If the other lesions meet the inclusion criteria, they will be treated according to the randomization assignment for the index study lesion. If they do not meet the inclusion criteria, they will be treated according to the discretion of the treatment team.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

All patients enrolled in the study will undergo post-operative SRS. This is a high-dose conformal radiation treatment delivered with high spacial precision using image-guided intensity-modulated radiation therapy equipment available at MSKCC, MGH, JHU, and Stanford. There is a wealth of published institutional experience with this treatment. This device is FDA-approved for this indication. The only difference to be assessed in this study will be in the fractionation pattern, with both single-fraction doses and hypofractionated doses having been safely used in the past. Dose constraints have been enumerated for single-fraction SRS (see Appendix G) and hypofractionated SRS (see Appendix H).

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- 1) Histologically diagnosed metastatic cancer (Diagnosis made or confirmed at MSKCC for MSKCC participants. Institutional pathologic determination accepted from participating multicenter sites.)
- 2) Age ≥ 18 years
- 3) Life expectancy ≥ 3 months
- 4) ECOG ≤ 3
- 5) Spinal surgery carried out with the goal of spinal cord decompression and spinal stabilization within 8 weeks
- 6) Post-operative CT myelogram or MRI perfusion with evidence of separation of tumor and the spinal cord

It should be noted that patients with multiple lesions will be eligible as long as there are no overlapping fields of radiation, including at various time frames.

6.2 Subject Exclusion Criteria

- 1) Primary spine tumor
- 2) Age < 18
- 3) Pregnancy
- 4) Lack of adequate (≥ 2 mm) separation between the spinal cord and the tumor on post-operative CT myelogram or MRI perfusion
- 5) Radiosensitizing chemotherapy (taxol, taxotere, cisplatin, gemcitabine, 5-fluorouracil) given within one week of radiation treatment

7.0 RECRUITMENT PLAN

Due note is taken of the NIH policy of inclusion of women and minorities in research protocols. Patients will not be excluded from the protocol based on gender, race or age. The study population will be representative of the range of patients undergoing post-operative SRS at the participating sites.

Potential subjects will be identified by a member of the patient's treatment team, the research team and/or the protocol investigators at MSKCC, MGH, JHU, or Stanford. All subjects for this study will be recruited from a pool of patients of the investigators. Subjects who appear to be eligible will be presented with the opportunity to participate. The study will be posted on the clinicaltrials.gov website. Furthermore, the trial will be posted on the MSKCC website under clinical trials.

Patients will be approached and consented anytime between the pre-operative discussion about surgery and the start of SRS treatment planning. Once the post-operative CT myelogram or MRI perfusion demonstrates separation of tumor and the spinal cord and all of the inclusion criteria are met, the patient will be randomized before the start of radiation treatment planning to receive either single-fraction or hypofractionated SRS within 8 weeks of surgery. The recruiting physicians will be familiar with the patient's medical history and health status at the time of recruitment since they will be directly involved in the post-operative radiation planning and will not require a waiver of authorization. Screening for the eligibility will not require collection of any additional patient information since all of the information required to determine patient eligibility will be required in order to appropriately plan the post-operative SRS.

Patients will not be recruited outside of the post-operative treatment pathway and no advertisement or patient compensation will take place.

8.0 PRETREATMENT EVALUATION

Pretreatment evaluations may be performed within 8 weeks of consent, and include the following:

- 1) Complete patient history
- 2) Complete neurologic and physical exam (specifically assessment of: skin including incision site, motor/sensory function, and ambulatory status)
- 3) Pathology review confirming metastatic cancer
- 4) MDASI (optionally)

- 5) BPI (optionally)
- 6) ECOG \leq 3
- 7) Current medications
- 8) Post-operative CT myelogram or MRI perfusion
- 9) Serum pregnancy test for women of child-bearing potential

9.0 TREATMENT/INTERVENTION PLAN

Patients will undergo SRS treatment simulation in supine position following a CT myelogram or MRI perfusion. They will be immobilized in the custom-fitted cradle which will be used for the duration of their treatment. A thermoplastic mould mask will be used for lesions above T4. Target volume contouring will be done according to the guidelines proposed by the International Spine Radiosurgery Consortium³⁸. The gross tumor volume (GTV) will be contoured according to standard institutional practice to include the entire tumor visible on any of the pre- or post-operative imaging studies, including MRI and CT. Every attempt will be made to include the entire preoperative tumor volume into the GTV even if a part or all of it were resected during surgery. The clinical tumor volume (CTV) will be expanded to include all of the adjoining marrow spaces in the vertebral body as defined by Cox et al³⁸. The planned treatment volume (PTV) will be expanded 2-3 mm around the CTV, but will not include the spinal cord. The spinal cord as defined on the CT myelogram or MRI perfusion will be excluded from all treatment contours. Inverse treatment planning will be carried out with the goal of maximizing the percentage of PTV receiving the 100% of the planned dose with a requirement of PTV V100 \geq 80%. GTV Dmin >15 Gy will be required with a goal V100 > 90%. The prescribed dose will be normalized to the 100% isodose line or its equivalent, depending upon institutional practices. In order to account for variability of delivery systems, doses will be prescribed that are equivalent to the absolute dose stipulated in the protocol. Volumetric modulated arc therapy (VMAT) may potentially be utilized. In order to ensure homogeneity of treatment plans among institutions, the first three treatment volumes from each institution will be reviewed by representatives from each institution and differences in contouring will be discussed in order to arrive at consensus.

Treatment will be administered using 6- and/or 15-MV photons using 7-9 coplanar beams with dynamic multi-leaf collimation. At the time of treatment, a three-dimensional kilovoltage cone-beam CT image obtained once the patient is positioned will be used to match the vertebral anatomy to the simulation scan and immediately before treatment patient alignment will be checked using two-dimensional kilovoltage verification. In case of 2mm or larger deviation, patient will be repositioned.

The organ at risk tolerances will be different for the two treatment arms and are presented in Appendix G (Single-Fraction) and Appendix H (Hypofractionated). The single-fraction treatment will be administered in one day while the hypofractionated treatment will be administered every other day. Total treatment time per fraction including set up will be 60-75 minutes per fraction.

Nausea, dysphagia and diarrhea will be treated according to standard institutional practice.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Pre-treatment evaluations may be performed within 8 weeks of consent. After SRS, patients will be closely monitored for any evidence of toxicity, systemic illness or tumor progression. Acute toxicity assessment (see Appendix E) will occur by phone or clinic visit within 4 weeks (± 10 days) after the completion of radiotherapy. Follow-up clinic visits will take place 3 months, 6 months, 9 months, 12 months, 18 months and 24 months (± 8 weeks) after the completion of radiotherapy. At each follow-up visit, the investigators will complete the Spine Clinic Assessment form (see Appendix F). Spine MRI or CT will also be performed at the time of each follow-up, in accordance with routine standard of care.

Table 1: Pre-therapy and Follow-up Evaluations

Item	Pre-therapy (w within 8 weeks of consent)	Follow-up (3, 6, 9, 12, 18, 24 months \pm 8 weeks after the completion of SRS)
Inclusion/exclusion criteria	X	
CT myelogram or MRI perfusion	X	
Pathology diagnosis confirming metastatic disease	X	
Medical history	X	
Pregnancy test ¹	X	
Physical exam	X	X
Concomitant medications review	X	X
ECOG	X	X
Quality of Life assessments (MDASI and BPI) ²	X	X
Spine Clinic Assessment Form	X	X
MRI/CT scan ³	X	X
Adverse-event/toxicity assessment ⁴	X	X
Consent	X	

¹ For women of child-bearing potential, a urine or blood pregnancy test must be completed within 2 weeks prior to SRS.

- ² Patients will be asked to complete quality of life (MDASI and BPI) assessments at all timepoints, however this will remain optional. In instances where these questionnaires are not available in the participant's primary language, the participant will not be required to complete the questionnaire(s).
- ³ All patients are required to have MRI/CT based imaging at baseline and 3, 6, 9, 12, 18, and 24 months (\pm 8 weeks) after SRS. The imaging modality should remain constant for each patient throughout.
- ⁴ Only treatment-related adverse events will be reported. Acute toxicity assessment (see Appendix E) will occur by phone or clinic visit within 4 weeks (\pm 10 days) after the completion of radiotherapy.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Toxicities/Complications

Subjects will be monitored for surgical complications. Our retrospective study found that major surgical complications occurred in 14.3% patients within 30 days of surgery. Among those patients that suffered complications from surgery within 30 days, Table 2 below depicts the likelihood of complications^{6,39}:

Table 2: Postoperative Complications

wound infection/dehiscence	2.9%
hardware fracture	2.8%
pneumonia	2.1%
pulmonary embolism	2.1%
postop hematoma	0.7%
radiculopathy	0.7%
stroke	0.7%
gastrointestinal bleed	0.7%

Cerebrospinal fluid leak is a rare complication, occurring after less than 5% of operations. Neurologic injury is an exceedingly rare post-operative complication, occurring after far less than 1% of operations.

Patients will also be monitored for radiation toxicity including: acute (\leq 90 days from the start of treatment) and late ($>$ 90 days) toxicity. All patients are going to be monitored for skin, subcutaneous tissue, spinal cord and fracture toxicity. In addition, patients undergoing cervical radiation will be monitored for mucous membrane, pharynx and esophagus, larynx and upper GI toxicity. Patients undergoing thoracic radiation will be monitored for upper and lower GI, lung and heart toxicity. Patients undergoing lumbar radiation will be monitored for genitourinary and lower GI toxicity. The severity of the toxicity will be graded according to Appendix I (Acute Radiation Toxicity) and Appendix J (Late Radiation Toxicity) based on the Radiation Therapy Oncology Group classification schema.

Low-grade radiation-related toxicity may include fatigue, skin erythema, subcutaneous fibrosis and bone pain. More significant toxicity is rare ($<$ 1%) and may include esophagitis,

pericarditis, diarrhea, nausea, vomiting, myelosuppression, myelitis, acute radiation pneumonitis, late pulmonary fibrosis, esophageal stricture, small bowel obstruction and radiation enteritis.

Participants should not be or become pregnant during the course of treatment because the radiation used in this study may be teratogenic. Participating sites should notify the MSK PI if an external participant becomes pregnant.

11.2 Adverse Events (AE)

Defined

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after treatment. For this study, we consider reportable adverse events to include radiation Grade 3 (and above) toxicity as enumerated in Section 11.1. Adverse events should be reported to both the site PI and the MSK PI, please see Section 16.0.3.

Reporting Requirements

For non-serious adverse events, we will only be capturing toxicities that are possibly related to study participation. Adverse event monitoring will be continued for 24 months following the completion of SRS treatment or until the time of death if death occurs prior to the 24 month follow-up. Adverse events should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event. Adverse events will be reported within 14 days.

Adverse events will be assessed by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (<http://ctep.info.nih.gov>). If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used.

As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (start and end dates or Ongoing at End of Study)
3. Its relationship to the study treatment (reasonable possibility that AE is related to study: No, Yes)
4. Action taken with respect to study (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a SAE is defined as in Section 17.2 (SAE)

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event form in CRDB. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary study endpoint, which is local tumor control, will be radiographically determined according to routine standard of care post-surgical and post-treatment imaging (MRI or CT) of the spine. Local tumor control will be defined as the lack of local tumor progression at the irradiated site on follow-up imaging. All imaging studies from collaborating institutions will be submitted for central review at MSK. T1, T1 gadolinium enhanced, T2 and STIR MR sequences will be used for follow-up imaging in order to monitor treatment response. 3-5mm slice thickness on MR imaging will be used. We will avoid strict imaging parameter restrictions since several medical centers will take part in the study and it will be challenging to strictly confine imaging criteria. Standard MRI sequences will be sufficient in order to monitor for recurrence. Volumetric measurements will not be used in this protocol. CT will be used in patients who cannot undergo MR imaging.

Each month, the imaging studies from participating sites will be batched and submitted through MSK's FTP Imaging Secure File Transfer system to the MSK PI. These scans should be de-identified prior to submission to MSK. The study RSA will transfer images to MSK's electronic Research PACS system. Central review will be carried out at two week intervals by MSK neuroradiologists (Dr. Eric Lis and Dr. Sasan Karimi) with expertise in interpretation of spinal oncology imaging. In cases of disagreement of the initial radiology read and central review interpretation, the results will be discussed with the treating surgeon or radiation oncologist in order to reach agreement. Site investigators will be notified of the review results within 24 hours. The turn-around time for central imaging review will be 14 days. Progression will be defined quantitatively as a 15% increase in maximal horizontal and vertical diameter, when not accounted for by fracture or evolving treatment change. The duration of response will be measured as lack of progression on imaging or until the last follow-up visit.

Secondary endpoints will include clinical determination of MRC muscle strength assessment, ECOG, ASIA, and treatment-related toxicity at each follow-up visit.

Secondary endpoint comparison of quality of life between the two cohorts will be determined through optional patient-reported responses for the MDASI - Spine Tumor Module at each follow up visit. The MDASI Spine Tumor Specific Items (questions #14-18) will be scored separately as a Spine Tumor Symptom Severity scale.

Secondary endpoint comparison of pain control will be determined through optional patient-reported responses of the BPI. Pain severity at its worst (question #5) and the average of the pain interference (average of question #9) will serve as the pain endpoints.

12.1 CRITERIA FOR RADIOGRAPHIC TUMOR PROGRESSION

Local disease progression will be defined as evident in the following ways:

- New or progressive paraspinal or epidural 5% increase in enhancing soft tissue mass not accounted for by evolving post therapy change,
- New bone destruction not accounted for by collapse.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. They may also be discontinued from the study treatment and assessments at any time, at the discretion of the investigators. Specific reasons for discontinuing a subject from the study include:

- Patient inability or loss to follow-up
- Adverse events deemed significant by the investigators
- Protocol non-compliance
- Elective termination: A subject may withdraw consent at any point in the study
- Patient death

14.0 BIOSTATISTICS

The primary endpoint of this multicenter Phase III noninferiority study is the local tumor control after post-operative spinal stereotactic radiosurgery (SRS). A noninferiority study design is justified on the basis that both treatment options have their advantages and disadvantages with currently mixed data about the relative tumor control offered by hypofractionated and single-fraction SRS. Some data suggest that single-fraction SRS may offer superior local control and since only one treatment visit is required it is cheaper and more convenient for patients. On the other hand, data suggest that single-fraction treatment may be associated with a higher risk of vertebral body fractures, which is considered a treatment-related toxicity. Determining whether single-fraction SRS and hypofractionated SRS offer comparable local tumor control will allow physicians to make treatment decisions based on factors such as cost and toxicity risk.

Lack of local radiographic progression will be defined as local tumor control. Patients will be randomized in a 1:1 fashion and the local control in the two treatment arms (single-fraction SRS vs. hypofractionated SRS) will be assessed. The patients will be stratified according to participating center (MSK, MGH, JHH, Stanford), presence or absence of prior radiation history at the study level, and radioresistance of the primary tumor histology, with breast and prostate classified as radiosensitive and the remaining solid tumor metastases (i.e. melanoma, sarcoma, thyroid, renal, colorectal) classified as radioresistant.

An intent-to-treat, stratified log rank test will be used to test whether or not the single-fraction SRS arm is inferior to the hypofractionated (3 fractions in total) SRS arm in terms of the local control rate. To set up a formal test we will use the 1-year local control rate as the surrogate of the efficacy (assuming that the two survival curves follow exponential distributions) and allow a 10% inferior margin. From a clinical standpoint, the investigators agreed that a difference of less than 10% is not regarded as significant. On this basis, we permit a 10% inferior margin. I.e., we will test $H_0: P_1 \leq (P_2 - 10\%)$ vs $H_1: P_1 > (P_2 - 10\%)$, where P_1 and P_2 denote the 1-year local control rate for the single-fraction arm and the 3-fraction arm, respectively. To approximately assess the power of the test, we estimate that the 3-fraction arm will yield a 1-year local control rate around 85% based on interim preliminary data from a multicenter Phase III trial (Protocol 10-154), and set the type I error (that is, declare single-fraction arm noninferior while it is not) rate at 0.10. When the two arms have equal efficacy, i.e., $P_1 = P_2 = 85\%$, the power (that is, declare the single-fraction arm noninferior while it is) of this noninferiority test⁴⁰ is 80% when there are 75 patients in each arm. Besides, since deaths without local failure are likely, competing risk analysis will also be used to estimate the local control rates of the two arms over time. We plan to enroll 150 patients within 2 years. If a

patient has multiple eligible lesions, all of them will be treated within the randomized arm and each eligible lesion (non-contiguous lesions treated with a separate radiation contour) will be treated as a separate study unit. After the enrollment of the final patient, a 2-year follow up is planned. Three interim analyses are planned and will be conducted at the time of the DSMB annual review of the study. The O'Brien-Flemming boundary will be applied for assessing statistical significance. Specifically, the rejection regions in terms of the corresponding Z-scores are $Z > 3.09$, $Z > 2.06$, $Z > 1.63$ and $Z > 1.39$ for the three interim looks and the final look, respectively. We expect that very few patients will have multiple lesions and thus we do not plan to examine the correlation among multiple lesions from the same patients. Instead, the analysis of the primary endpoint will be conducted at lesion level as mentioned above. Data will be collected from all four centers and analyzed at MSKCC.

In consideration of the fact that a large cohort will be recruited, this study will be continuously monitored to protect patients from excess toxicity. For each arm, we anticipate that the true rate of any grade 4 toxicity within 24 months post SRS is less than 10%. All grade 4 toxicities or greater observed will be reviewed by the study chair. Moreover, using a stopping rule based on sequential probability ratio test (SPRT), each arm of the study is monitored for any grade 4 or above toxicities that are judged to be associated with the radiation treatment. This stopping rule specifies that for each arm, the study will be halted if any of the following conditions occur: >4 /first 15; >6 /first 35; >9 /first 55; or if more than 12 unacceptable toxicities are observed within 24 months post SRS when the last (75th) patient has completed the trial. When the true toxicity rate is 10%, this stopping rule has a probability of 0.1 to stop the trial. When the true toxicity rate is 20%, this stopping rule has a probability of 0.8 to stop the trial. For this stopping rule we will use each patient as a study unit.

Toxicity outcomes and patterns of complications are summarized and tabulated in Section 11.0. Comparisons will be made using Wilcoxon rank sum tests and proportion tests. QOL results measured by MDASI scores and pain control results measured by BPI scores will also be summarized and compared between the two arms by Wilcoxon rank sum tests. As multiple measurements will be taken and thus multiple tests will be conducted, test p-values will be adjusted by the false discovery rate method.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (<http://ppr/>). The completed signature page of the written consent/RA or

verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 For Participating Sites:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to email registration/eligibility documents per the contact information provided by the the MSK study coordinator. These documents must be sent via a secure, encrypted email.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation (containing a minimum of two patient identifiers such as date of birth and initials) for eligibility questions (pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

15.2 Randomization

Randomization will be centralized at MSKCC. Patients will be randomized to the single dose arm (24 Gy) or the multi-dose arm (27 Gy in 3 fractions). Ineligible lesions and other lesions not being treated on protocol will be treated according to standard of care at the physician's discretion. Immediately after consent is obtained at MSKCC and at participating sites, the RSA will register participants in the Protocol Participant Registration (PPR) system. Once the participant's eligibility is established, the registration will be finalized and the participants will

be randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and will be stratified by institution, prior radiation history, and radioresponsiveness of the primary disease site (radioresponsive tumors include prostate, lung, breast, etc and non-responsive tumors include melanoma, renal cell, colon and sarcoma). After the treatment arm is determined by randomization, the RSA will notify the research staff and/or investigators at MSKCC and participating sites of the treatment arm and participant ID via email within 24 hours of randomization.

Data will be collected at other centers and sent to the RSA(s) at MSKCC according to Table 6. Compiled data will be submitted to the biostatisticians at MSKCC for analysis.

16.0 DATA MANAGEMENT ISSUES

A designated Research Study Assistant will be responsible for accurate and confidential documentation, data recording, compliance, regulatory monitoring and coordination of activities of the study team. The data collected during this study will be handled in the same manner as all of patient health information in compliance with HIPAA regulations. All data collected during pre-enrollment assessment and during the course of the study will be entered into the Clinical Research Database (CRDB) Minimal Dataset. Data will be reported to the IRB every 6 months.

The data will also be collected in the Caisis database, with source information stored in the patient records.

List of variables and population characteristics:

- Patient demographic data (gender, date of birth, height, weight)
- Medical and surgical history
- Concomitant medication
- Toxicity
- AE's*
- Number and location of metastatic sites, as well as whether the sites are positive or negative on imaging
- Epidural Spinal Cord Compression (ESCC) score (0-3)⁴¹

*If an adverse event meets the criteria for an SAE, then an SAE report must be completed as per the instructions for SAE reporting in section 17.2.

16.0.1 Data and Source Documentation for Participating Sites

Data

The participating sites will enter data remotely into MSKCC's internet-based Clinical Research Database, termed CRDBi-Multicenter. In case of problems with the system, the MSKCC research team should be contacted directly. The site staff will receive CRDB training prior to enrolling its first participant. The participating Site PI is responsible for ensuring these forms are completed accurately and in a timely manner.

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter. Source documentation should be consistent with data entered into CRDBi-Multicenter. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre-protocol disease status
- Acute Toxicity Assessment Forms
- Spine Clinic Assessment Forms
- Treatment records
- Toxicities/adverse events not previously submitted with SAE Reports
- Response designation
- Radiology imaging via MSK's Secure File Transfer system
- Radiology reports

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into CRDBi- Multicenter. Source documentation should be sent to MSK at the contact information provided by the MSK study coordinator. Submissions should include a cover page listing relevant records enclosed per participant.

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to Table 6 below.

Table 6: Timelines/Requirements for Data and Source Documentation Submission

	Baseline	At completion of SRS	Follow-up*	SAE	Off Study
SUBMISSION SCHEDULE					
Source Documentation	Within 24 hours of registration	Within 14 days of completion of SRS	Within 14 days of visit	Within 3 days of knowledge of the event (see section 17.2.1); updates to be submitted as available	Within 14 days of participant removal
CRDBi-MCT	Within 7 days (see 15.1.1)				
REQUIRED FORMS (in CRDBi-MCT)					
Administrative	X				
Disease	X				
Pathology	X				
Medical History	X				
Physical Exam	X		X		
Concomitant Drug	X		X		X
Prior Therapy	X				
Surgery		X			
External Beam Radiation		X			
Outcome			X		X
Toxicity****		X	X	X	X
Spine Details	X		X		X
Diagnostic Test	To be submitted with other data forms whenever applicable				
Hospitalization	To be submitted whenever a hospitalization occurs, unless included in the SAE form				
Patient Status	To be submitted within Minimal Dataset whenever patient status changes				
Radiology Imaging Studies	X	X	X		
Radiology Reports	X	X	X		
QOL Assessments (MDASI/ BPI)**	X		X		
Acute Toxicity Assessment Form***	X		X		
Spine Clinic Assessment Form	X		X		X

*Follow-up visits: 3, 6, 9, 12, 18, 24 months (\pm 8 weeks) after the completion of SRS.

**QOL assessments will be requested at all timepoints, however this will remain optional.

***Acute Toxicity Assessment must occur within 4 weeks (\pm 10 days) after completion of SRS.

****Toxicities/adverse events that meet reporting requirements as outlined in section 11.

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Principal investigators will maintain complete and accurate medical and treatment histories in the patients' medical records. The data will be prospectively entered by the designated RSA into the Casis database at the time of enrollment and during the designated follow-up events. The RSA will assist the PI in data quality assurance. The RSA will confirm up-front registration of all subjects, verify eligibility by review of each case with the principal investigators at the time of enrollment, review records to confirm that informed consent is properly obtained and procedures are performed according to study protocol, and monitor protocol accrual. A weekly meeting with participation of the investigators and the RSA will be held in order to review the data collected each week and to address omissions and inconsistencies in the data to maintain compliance to the protocol.

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team.

16.1.1 Quality Assurance for Participating Sites

Each site accruing participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation.

Audits will be conducted annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by auditor availability and the complexity of the protocol. Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology will need to be obtained from the participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://inside2/dinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization

- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at the participating site

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing

participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRDBi-MCT data for 3 years.

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

There are no unforeseen additional risks to the patients from this study. Every effort will be made to protect the rights of human subjects in compliance with institutional policy. The risks

and benefits, potential toxicities and side effects will be thoroughly discussed with the patient at the time of enrollment. This discussion will largely be identical to the discussion that takes place at the time of treatment consent outside of the study, since the risks of participating in this study will be identical to the risks of post-operative radiation which would be administered outside of the study. Informed consent is a prerequisite to enrollment on the study. Enrollment in the study is entirely voluntary. It will be made clear that the patients have a right to refuse participation and that their care will not be adversely affected in case of refusal. Furthermore, the patients will have the right to withdraw from the study at any time, without any adverse consequences to their treatment. The patients will not incur any additional costs or burdens related to participation in the study.

In accordance with institutional policy, privacy and confidentiality of medical records will be strictly observed. All data pertaining to the study will also be likewise protected.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

This study defines Serious Adverse Event may include the following:

- any Grade 4-5 toxicity that is a direct result of protocol treatment, with the exception of vertebral body fracture which is a common occurrence after spinal radiosurgery and infrequently represents a significant adverse event
- any hospitalization within 30 days of treatment
- any hospitalization after 30 days of treatment if it is directly related to the protocol intervention.

Any SAE must be reported to the IRB/PB **as soon as possible but no later than 5 calendar days**. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred

- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report. Only one event will be captured as the cause of death. All SAEs and deaths that occur within the trial period or within 30 days after administration of the last dose of radiation therapy may be reported primarily for the purposes of serious adverse event (SAE) reporting, this includes deaths that are due to progression of disease.

All trial treatment-related toxicities and SAEs must be followed up until resolution.

17.2.1

17.3 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approval/acknowledgements must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report form found in MSK's internet based Clinical Research Database to MSK within 3 calendar days of learning of the event.
- When a death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event. **SAE contact information:**

Email: kahns@mskcc.org to the attention of 14-233 Research Staff

AND

Email: lauferi@mskcc.org

Responsibility of MSK

- MSK Research Staff are responsible for submitting all SAEs to the MSK IRB/PB as specified in 17.2.
- The MSK PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSK IRB/PB.
- The MSK PI is responsible for informing all participating sites within 24 hours or on the next business day about a death that is unforeseen and indicates participants or other are at increased risk of harm.

17.4 Safety Reports

MSK must submit external safety reports to the MKS IRB/PB according to institutional guidelines. All external safety reports will be made available to the participating sites. For those safety reports that require an amendment, the participating sites will receive a special alert.

Participating sites are responsible for submitting safety reports to their local IRB per their local IRB guidelines. All local IRB approvals/acknowledgements of safety reports must be sent to MSK upon receipt.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center.

The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 For Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

- 1 Bartels, R. H., van der Linden, Y. M. & van der Graaf, W. T. Spinal extradural metastasis: review of current treatment options. *CA Cancer J Clin* **58**, 245-259, doi:10.3322/ca.2007.0016 (2008).
- 2 Chaichana, K. L., Pendleton, C., Sciubba, D. M., Wolinsky, J. P. & Gokaslan, Z. L. Outcome following decompressive surgery for different histological types of metastatic tumors causing epidural spinal cord compression. Clinical article. *Journal of neurosurgery. Spine* **11**, 56-63, doi:10.3171/2009.1.spine08657 (2009).
- 3 Hirabayashi, H. *et al.* Clinical outcome and survival after palliative surgery for spinal metastases: palliative surgery in spinal metastases. *Cancer* **97**, 476-484, doi:10.1002/cncr.11039 (2003).
- 4 Finkelstein, J. A. *et al.* A population-based study of surgery for spinal metastases. Survival rates and complications. *J Bone Joint Surg Br* **85**, 1045-1050 (2003).
- 5 Falicov, A. *et al.* Impact of surgical intervention on quality of life in patients with spinal metastases. *Spine (Phila Pa 1976)* **31**, 2849-2856, doi:10.1097/01.brs.0000245838.37817.40 (2006).
- 6 Wang, J. C. *et al.* Single-stage posterolateral transpedicular approach for resection of epidural metastatic spine tumors involving the vertebral body with circumferential reconstruction: results in 140 patients. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. *Journal of neurosurgery. Spine* **1**, 287-298, doi:10.3171/spi.2004.1.3.0287 (2004).
- 7 Witham, T. F., Khavkin, Y. A., Gallia, G. L., Wolinsky, J. P. & Gokaslan, Z. L. Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. *Nat Clin Pract Neurol* **2**, 87-94; quiz 116, doi:10.1038/ncpneuro0116 (2006).
- 8 Laufer, I. *et al.* The NOMS framework: approach to the treatment of spinal metastatic tumors. *Oncologist* **18**, 744-751, doi:10.1634/theoncologist.2012-0293 (2013).
- 9 Lau, D., Leach, M. R., La Marca, F. & Park, P. Independent predictors of survival and the impact of repeat surgery in patients undergoing surgical treatment of spinal metastasis. *Journal of neurosurgery. Spine* **17**, 565-576, doi:10.3171/2012.8.spine12449 (2012).
- 10 Laufer, I., Hanover, A., Lis, E., Yamada, Y. & Bilsky, M. Repeat decompression surgery for recurrent spinal metastases. *Journal of neurosurgery. Spine* **13**, 109-115, doi:10.3171/2010.3.spine08670 (2010).
- 11 Patchell, R. A. *et al.* Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* **366**, 643-648, doi:10.1016/s0140-6736(05)66954-1 (2005).
- 12 Laufer, I. *et al.* Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: outcome analysis in 186 patients. *Journal of neurosurgery. Spine* **18**, 207-214, doi:10.3171/2012.11.spine12111 (2013).
- 13 Gerszten, P. C., Burton, S. A., Ozhasoglu, C. & Welch, W. C. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976)* **32**, 193-199, doi:10.1097/01.brs.0000251863.76595.a2 (2007).
- 14 Gerszten, P. C., Mendel, E. & Yamada, Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? *Spine (Phila Pa 1976)* **34**, S78-92, doi:10.1097/BRS.0b013e3181b8b6f5 (2009).
- 15 Rades, D. *et al.* Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **24**, 3388-3393, doi:10.1200/JCO.2005.05.0542 (2006).
- 16 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* **79**, 524-530, doi:10.1016/j.ijrobp.2009.10.073 (2011).
- 17 Maranzano, E. & Latini, P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. *Int J Radiat Oncol Biol Phys* **32**, 959-967 (1995).
- 18 Maranzano, E. *et al.* Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **23**, 3358-3365, doi:10.1200/JCO.2005.08.193 (2005).
- 19 Gilbert, R. W., Kim, J. H. & Posner, J. B. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Ann Neurol* **3**, 40-51, doi:10.1002/ana.410030107 (1978).
- 20 Katagiri, H. *et al.* Clinical results of nonsurgical treatment for spinal metastases. *Int J Radiat Oncol Biol Phys* **42**, 1127-1132 (1998).
- 21 Yamada, Y. *et al.* High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys* **71**, 484-490, doi:10.1016/j.ijrobp.2007.11.046 (2008).
- 22 Fuks, Z. Engaging the vascular component of the tumor response. *Cancer cell* **8**, 89-91, doi:10.1016/j.ccr.2005.07.014 (2005).
- 23 Garcia-Barros, M. *et al.* Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* **300**, 1155-1159, doi:10.1126/science.1082504 (2003).
- 24 Ch'ang, H.-J. ATM regulates target switching to escalating doses of radiation in the intestines. *Nature medicine* **11**, 484-490, doi:10.1038/nm1237 (2005).
- 25 Yamada, Y. *et al.* in *International Journal of Radiation Oncology, Biology, Physics*. S132-133.
- 26 Garg, A. K. Phase 1/2 trial of single-session stereotactic body radiotherapy for previously unirradiated spinal metastases. *Cancer* **118**, 5069-5077, doi:10.1002/cncr.27530 (2012).
- 27 Chang, E. L. *et al.* Phase III study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *Journal of neurosurgery. Spine* **7**, 151-160, doi:10.3171/SPI-07/08/151 (2007).
- 28 Kavanagh, B. D., Miften, M. & Rabinovitch, R. A. Advances in treatment techniques: stereotactic body radiation therapy and the spread of hypofractionation. *Cancer journal* **17**, 177-181, doi:10.1097/PPO.0b013e31821f7dbd (2011).
- 29 Wang, X. S. *et al.* Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1-2 trial. *Lancet Oncol* **13**, 395-402, doi:10.1016/s1470-2045(11)70384-9 (2012).
- 30 Terezakis, S. A. *et al.* Image-guided intensity-modulated photon radiotherapy using multifractionated regimen to paraspinal chordomas and rare sarcomas. *Int J Radiat Oncol Biol Phys* **69**, 1502-1508, doi:10.1016/j.ijrobp.2007.05.019 (2007).
- 31 Sahgal, A. *et al.* Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. *Int J Radiat Oncol Biol Phys* **85**, 341-347, doi:10.1016/j.ijrobp.2012.05.007 (2013).
- 32 Cox, B. W. Esophageal toxicity from high-dose, single-fraction paraspinal stereotactic radiosurgery. *International journal of radiation oncology, biology, physics* **83**, e661-667, doi:10.1016/j.ijrobp.2012.01.080 (2012).
- 33 Sahgal, A. *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* **31**, 3426-3431, doi:10.1200/jco.2013.50.1411 (2013).
- 34 Cleeland, C. S. *et al.* Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* **89**, 1634-1646 (2000).
- 35 Kirkova, J. *et al.* Cancer symptom assessment instruments: a systematic review. *J Clin Oncol* **24**, 1459-1473, doi:10.1200/jco.2005.02.8332 (2006).
- 36 Atkinson, T. M. *et al.* The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations. *Pain Med* **11**, 337-346, doi:10.1111/j.1526-4637.2009.00774.x (2010).

- 37 Cleeland, C. S. & Ryan, K. M. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* **23**, 129-138 (1994).
- 38 Cox, B. W. *et al.* International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *International journal of radiation oncology, biology, physics* **83**, e597-605, doi:10.1016/j.ijrobp.2012.03.009 (2012).
- 39 Amankulor, N. M. *et al.* The incidence and patterns of hardware failure after separation surgery in patients with spinal metastatic tumors. *Spine J*, doi:10.1016/j.spinee.2013.10.028 (2013).
- 40 Jung, S. H., Kang, S. J., McCall, L. M. & Blumenstein, B. Sample size computation for two-sample noninferiority log-rank test. *J Biopharm Stat* **15**, 969-979, doi:10.1080/10543400500265736 (2005).
- 41 Bilsky, M. H. *et al.* Reliability analysis of the epidural spinal cord compression scale. *Journal of neurosurgery. Spine* **13**, 324-328, doi:10.3171/2010.3.SPINE09459 (2010).

20.0 APPENDICES

Appendix A: MD Anderson Symptom Inventory (MDASI) – Spine Tumor

Appendix B: MD Anderson Symptom Inventory (MDASI) User Guide

Appendix C: Brief Pain Inventory (BPI)

Appendix D: Brief Pain Inventory (BPI) User Guide

Appendix E: Acute Toxicity Assessment Form

Appendix F: Spine Clinic Assessment Form

Appendix G: MSKCC Single-fraction SRS Plan Evaluation Criteria

Appendix H: MSKCC Hypofractionated SRS Plan Evaluation Criteria

Appendix I: Acute Radiation Toxicity

Appendix J: Late Radiation Toxicity