PHASE IV TRIAL EVALUATING THE USE OF STEREOTACTIC BODY RADIOTHERAPY FOR THE TREATMENT OF SPINE METASTASES AND PRIMARY SPINE TUMORS

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SCHEMA

R	Stereotactic Body Radiotherapy (SBRT)	
E	Patient Groups:	Vertebral Metastasis - not previously irradiated
		Vertebral Metastasis - previously irradiated cord
G		Intramedullary Spinal Metastasis
I	Suggested Dose-Fractionation:	14-25 Gy / 1 fraction
		21-27 Gy / 3 fractions (7-9 Gy per fraction)
S		25-30 Gy / 5 fractions (5-6 Gy per fraction)
T	Patient Group:	Benign Extradural Spinal Tumor
E	Suggested Dose-Fractionation:	12-16 Gy / 1 fraction
		21-27 Gy / 3 fractions (7-9 Gy per fraction)
R		25-30 Gy / 5 fractions (5-6 Gy per fraction)

Chemotherapy

Chemotherapy may be given at the discretion of the patient's medical oncologist. However, ideally chemotherapy should not have been given within 30 days of starting radiation and should not resume until at least 2 weeks after completing radiation. In addition, it is not recommended to perform SBRT when targeted anti-angiogenesis therapy is planned within 2 months of the procedure.

Eligibility

- Patient age $\geq$ 18 years
- Zubrod performance status of 0-3
- Vertebral and/or paraspinal metastases, with or without prior surgery and/or fractionated radiotherapy
- Benign extradural spine tumors, such as chordomas, meningiomas, schwannomas, neurofibromas, paragangliomas, and arteriovenous malformations (AVMs).
- Established histologic diagnosis of a benign or malignant tumor of the spine. For patients with malignant spine tumors, the histologic diagnosis may come from biopsy of the primary tumor site or an elsewhere metastatic site. If this represents the first appearance of metastatic disease, however, the diagnosis of metastasis should be histologically confirmed, when possible
- Arteriovenous malformation (AVM) of the spine identified radiographically (no biopsy required)
- Well-defined lesion involving no more than 2 adjacent vertebral levels or spinal segments
- No overt spinal instability
- Neurologic deficit is unrelated to bony fragments/bony compression of neural structures
- No previous radiation therapy at the involved level(s) within 3 months of radiosurgery
- Minimal spinal canal compromise that is not rapidly progressive
- No pregnant or lactating women (negative pregnancy test for women of child-bearing age)
- Signed study-specific consent form

1.0 Introduction

Spine metastases are a common pattern of spread for many different malignancies, especially prostate cancer, breast cancer, lung cancer, renal cancer, melanoma, and colorectal cancer. Treatment of symptomatic spine metastases typically consists of radiation therapy, sometimes following surgical decompression of the spine. Radiation therapy has been used to improve tumor control, alleviate tumor-related pain, prevent pathologic fractures, and improve neurologic symptoms such as weakness, numbness, and paresthesias. The traditional radiation therapy course consists of daily treatment, Monday through Friday, for a period of approximately 2-5 weeks. A prolonged course of radiation therapy can affect quality of life, particularly if life expectancy is limited. In addition, patients with spinal metastases often have other sites of disease, and a more rapid radiation course may allow more timely administration of systemic chemotherapy to address these other disease sites. Recent technological advancements allow high-dose precisely targeted radiation treatments to be delivered in only 1-5 sessions. A more rapid radiation course may positively affect quality of life. This radiation procedure is called stereotactic body radiotherapy (SBRT). Traditional radiation therapy usually includes at least 1-2 vertebral levels proximal and distal to the affected spine. SBRT limits the amount of normal tissue irradiated, and this sparing of bone marrow may facilitate continued delivery of intensive systemic chemotherapy with less delays for management of myelosuppression. Radiosurgery may also result in better long-term local control than standard radiation therapy thus obviating the ultimate need for extensive spine surgery for decompression and fixation, and may provide potentially more rapid onset of clinical response such as pain improvement or amelioration of neurologic deficits.

Treatment of recurrent spine metastases is often challenging. With the advent of more effective chemotherapy and targeted therapy agents, many patients with metastatic cancer are surviving longer than has traditionally been seen in the past. Although patients often have significant improvement in pain and/or neurologic symptoms with traditional radiation therapy, as survival rates have improved patients are at risk of developing recurrent symptomatic disease. Traditional radiation therapy cannot be repeated at the same site in the spine, due to the increased risk of injury to normal tissue. Spinal surgery is often difficult and can be associated with significant risk, or may not be an option due to prior surgery, other medical conditions or limited life expectancy. Stereotactic body radiotherapy offers an alternative to surgery for management of recurrent disease, which can be delivered in an outpatient setting with low risk of side effects.

Treatment of primary spine tumors may consist of surgery, radiation therapy, or a combination of surgery followed by radiation therapy. As with spine metastases, radiation therapy has been used to achieve tumor control, alleviate tumor-related pain, and improve neurologic symptoms such as weakness, numbness, and paresthesias. The traditional radiation therapy course consists of daily treatment, Monday through Friday, for a period of approximately 3-6 weeks. This prolonged course of radiation can affect quality of life. Stereotactic body radiotherapy (SBRT) allows the delivery of highly precise radiation in only 1-5 treatments. Surgical management of patients with primary spine tumors can be associated with significant risk of morbidity. Some patients are not surgical candidates due to other serious medical conditions. The advantage of SBRT over surgery is that it is not painful, and does not require anesthesia or hospitalization. In addition, some of these benign tumors, such as meningiomas and schwannomas, also occur in the brain where radiosurgery has been proven to produce local control rates similar to surgical resection.

Traditional fractionated radiation therapy for spine metastases has been studied extensively. A meta-analysis of 16 randomized trials comparing various schedules of fractionated radiation therapy over 1-2 weeks to single fraction radiotherapy demonstrated unsatisfactory complete pain relief rates of less than 30%. Most studies analyzed used a single fraction of 8 Gy. There was no difference between single fraction and multi-fraction radiotherapy in overall response rate or complete response rate; however, the

re-treatment rate was 2.5 fold higher for single fraction radiation therapy (1). The dose that can be delivered safely in a single fraction of radiation to the spine is limited by the tolerance of the spinal cord. Standard radiation therapy commonly includes a relatively long length of spinal cord, and delivers the full prescription dose to the cord.

Recent technological advances have made it possible to deliver high doses of radiation therapy with high precision over just a few days, while preserving function of surrounding critical structures. This treatment modality, termed stereotactic body radiotherapy (SBRT), is emerging as an expedient, safe, and effective radiation modality for a variety of malignancies. SBRT was recently defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) as a "treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body" (2). Stereotactic radiosurgery is a well-established treatment for intracranial metastases with local control rates of 80-90%. Several institutions have investigated the use of SBRT for the treatment of spine metastases and primary spine tumors, and have reported excellent local tumor control, onset of pain relief and neurologic improvement at least as rapid as traditional radiation therapy, with fairly low toxicity risk. Many phase I and II trials of SBRT have now been published demonstrating its efficacy and safety. Although follow-up is variable, the local control rates for metastatic disease have generally been in the range of 81-95%, at least partial pain relief of 67-100%, and rates of late myelopathy of 0-4%. No grade 3-5 late toxicity has been reported with respect to other organs such as the kidneys, lungs, bowel, and esophagus (3).

Gerszten and colleagues from the University of Pittsburgh published a series of 393 patients with 500 spine metastases treated with Cyberknife stereotactic radiosurgery to a maximum dose of 12.5-25 Gy (mean 20 Gy, or 16 Gy to the 80% isodose line) in a single fraction. 344 tumor sites had received prior fractionated radiation therapy (30 Gy in 10 fractions or 35 Gy in 14 fractions). With a median follow-up of 21 months, 86% had significant long-term pain improvement and 88% had long-term tumor control. The rate of neurologic deficit improvement was 84%. No tumor progression at immediately adjacent spine levels was seen. There were no cases of treatment-related myelopathy (4).

Some tumor histologies, such as renal cell carcinomas and malignant melanoma, are known to be relatively radioresistant, and thus standard RT may provide less than optimal clinical response. The University of Pittsburgh experience treating spine metastases from renal cell cancer and malignant melanoma was reported by Gerszten in 2005. Forty-eight patients with 60 renal cell metastases were treated to 14-20 Gy (mean 16 Gy) prescribed to the 80% isodose line (maximum dose 17.5-25 Gy) in a single fraction. Most patients had previously been treated with fractionated external-beam radiation therapy. With a median follow-up of 37 months, 89% of patients had durable pain improvement and there were no cases of radiation myelopathy or radiculopathy (5). Thirty-six melanoma spine metastases in 28 patients were treated with single fraction SBRT using the same dose regimen. With a median follow-up of 13 months, 96% of patients had long-term pain improvement and there were no cases of neural toxicity (6).

Chang and colleagues published MD Anderson Cancer Center's phase I/II experience using SBRT for spine metastases. Seventy-four tumors in 63 patients were treated to 30 Gy in 5 fractions or 27 Gy in 3 fractions delivered every 2 days, with typically 80-90% of the target volume receiving at least the prescription dose. Thirty-five patients had previously received in-field radiation therapy, with the cord dose limited to < 45 Gy. No chemotherapy was given within 30 days of radiosurgery. With a median follow-up of 21.3 months, the 1-year local control rate based on MRI imaging was 84%, and narcotic use decreased from 60% to 36% at six months. Twenty-three percent of patients progressed radiographically, and the pattern of failure suggested that the pedicles and posterior elements using a wide bone margin posterior to the involved vertebrae should be routinely included in the planning target volume. The spinal

cord was limited to 10 Gy in 5 fractions or 9 Gy in 3 fractions. No patient developed grade 3 or 4 neurologic toxicity (7).

Yamada and colleagues from Memorial Sloan-Kettering Cancer Center treated 103 spinal metastases in 93 patients with SBRT to a median dose of 24 Gy (range 18-24 Gy), with the median percentage of the PTV receiving at least 95% of the dose being 95% (82-100%). No patient had received prior RT to the region of interest. The maximum spinal cord dose was limited to 14 Gy and the cauda equina dose was limited to 16 Gy. With a median follow-up of 15 months, 90% of patients experienced durable pain control and local control. The median time to local failure was 9 months. Local control was dose-related: 95% for 24 Gy compared to 80% for < 24 Gy (mean 20.8 Gy). Treatment failure was defined as disease progression on MRI. Acute toxicity was generally mild (grade 1-2), and there were not cases of late myelopathy or radiculopathy (8).

The Stanford University experience was reported by Gibbs and colleagues. Seventy-four patients with 102 spinal metastases were treated with Cyberknife. The majority (50 patients) had prior radiation therapy within or adjacent to the treatment site. Patients were treated to 16-25 Gy in 1-5 fractions, with fractionated treatment used when single-fraction SBRT would give a cord Dmax > 10 Gy. With a mean follow-up of 9 months, 84% had improvement or resolution of their symptoms and 3 patients (4%) developed clinical or radiographic signs of spinal cord injury at 6-10 months after treatment. There were no clear spinal cord total dose or average dose that predicted these complications. Two of three patients had received anti-angiogenic or epidermal growth factor inhibitor-targeted therapy within 2 months of developing clinical myelopathy. No complications occurred when the volume of cord receiving a biological equivalent dose of 12 Gy in a single fraction (BED_3 of 58 Gy) was less than 0.15 cm^3. Acute toxicity was uncommon and limited to nausea. They recommended using SBRT treatment schedules that limited the spinal cord biologic equivalent dose to 10 Gy to $\leq$ 0.3 cc and 12 Gy to $\leq$ 0.15 cc in 1 fraction (9).

The Stanford University experience in treating benign tumors of the spine has been reported. Fifty-one patients with 55 benign extra-axial, intradural spinal tumors were treated with Cyberknife stereotactic radiosurgery, including 30 schwannomas, 9 neurofibromas, and 16 meningiomas. Only 4 patients were previously irradiated. Eligibility criteria were contraindications for surgery due to medical co-morbidities, underlying Neurofibromatosis I (7 patients) or II (10 patients) resulting in multiple lesions developing over time, or patient preference, with well-circumscribed lesions, no evidence of spinal instability and minimal compression of the spinal cord. The most common presenting symptom was pain, followed by radiculopathy and myelopathy. Patients were treated to 16-30 Gy in 1-5 fractions typically to the 80% IDL (most received 1-2 fractions). The median follow-up time was 23 months. Of the 28 patients with greater than 24 months follow-up, all have stabilized (61%) or decreased (39%) in size. Radiosurgery was not very effective at reversing mass effect. Three tumors enlarged by < 10% at 6-12 months, two were transient and one underwent surgery for worsening pre-existing meylopathy. Schwannoma patients experienced 96% local control, with 56% stable and 40% decreased in size on imaging. The majority experienced stabilized clinical symptoms, 50% had significant pain improvement, and 40% had decreased weakness or improved sensation; 18% experienced clinical worsening. Meningioma patients experienced 100% local control, with 67% stable and 33% decreased in size on imaging. Approximately 70% significant improvement in pain and 50% had improved strength, but without improvement in sensory loss. Thirty percent experienced minor worsening pain, numbness, or weakness. Only 50% of neurofibroma patients were symptomatically stable, and none had improved clinical symptoms. However, 6 of 7 patients who underwent follow-up imaging had stable disease. Interesting, the surgical literature also reports poor symptomatic control. One patient with a meningioma (2%) experienced presumed radiation myelopathy 8 months after SBRT to a dose of 24 Gy in 3 fractions (maximum dose 3435 cGy); the volume of cord irradiated to 18 Gy was 1.7 cm^3 (9,10).

Intramedullary spinal cord AVMs have also been treated with SBRT. A report from Stanford University on 15 patients treated to a mean prescription dose of 20 Gy in 2-5 fractions. With mean follow-up of 28 months, only 1 of 8 patients with follow-up angiography at 3 years showed complete obliteration; however, there were no further hemorrhages or neurologic deterioration. The authors recommended not treating intramedullary lesions greater than 1.5 cm^3 in volume, to minimize the chance of neural toxicity (9).

Sohn (from Korea) reported results at the International Stereotactic Radiosurgery Society Meeting in July 2007 on the use of SBRT for 33 patients with schwannoma or meningioma of the spine treated with the Novalis system. Patients received a single fraction of 13 Gy (schwannoma) or 15 Gy (meningioma) prescribed to the 80% isodose line. For patients with spinal cord compression, fractionated stereotactic radiosurgery was utilized (24 Gy in 3 fractions). With a mean follow-up of two years, there were no late toxicities.

Also at the International Stereotactic Radiosurgery Society Meeting in July 2007, Sahgal (UCSF) reported the results of 16 patients with benign spinal tumors treated with Cyberknife radiosurgery. Doses ranged from 12 Gy in 1 fraction to 5 Gy in 5 fractions. With a median follow-up of 25 months, there were no late toxicities. Three patients with Neurofibromatosis I progressed. The one year freedom from progression rate was 89%.

St. John's Mercy has installed an Elekta Synergy-S® linear accelerator at the David C. Pratt Cancer Center that is specifically designed to deliver highly-precise SBRT treatments. It has a tightened isocenter accuracy calibrated to a precision of within 1.5 mm diameter, a micro-MLC for treatment of small radiation ports, a specially designed Hexapod® table top that can correct for patient misalignment in both translational and rotational directions, an onboard cone-beam kV CT for precise tumor localization immediately prior to treatment, four-dimensional CT (4D-CT) and 3D Line® which together allow for accurate monitoring of and compensation for tumor motion during respiration, active breathing control for respiratory gating, and real-time continuous fluoroscopic capability for visual confirmation that the target remains in the treatment field.

2.0 Objectives

This study will evaluate the local control rate as well as acute and late toxicity rates of stereotactic body radiotherapy (SBRT) for the treatment of spine metastases and benign spine tumors.

2.1 Hypothesis

2.1.1 For selected patients with spine metastases or benign spine tumors, stereotactic body radiotherapy (SBRT) is technically feasible with acceptable complication rates.

2.1.2 Local tumor control rate with stereotactic body radiotherapy (SBRT) will be at least as good as standard fractionation radiation therapy.

2.2 Study Design

2.2.1 Single site, non-randomized, prospective, phase IV trial

2.2.2 Composed of 2 patient groups:
Spine Metastases
Benign Spine Tumors

2.2.3 Data collected will include patient demographics, pathology data, tumor stage, SBRT dose fractionation scheme, dose received by adjacent critical normal tissues, tumor recurrence data, and acute and late toxicities.

2.2.4 Follow up data will be collected during the patient's standard office visits. The anticipated duration of this study is 5 years.

2.3 End Points

2.3.1 Primary endpoints will be symptom control and local tumor recurrence rate.

- Evaluation of pain relief will be assessed using a 10-point visual analog scale
- Analgesic use will be documented to ensure that pain improvement is not due to an increase in the amount of analgesic usage.
- Evaluation of neurologic improvement will be assessed by physical exam using the ASIA Impairment Scale
- Local recurrence is defined as tumor recurrence or progression within the planning target volume.
- Local control rate will be evaluated by imaging techniques and/or clinical symptoms (worsening or no improvement in pain or neurologic compromise). If follow-up imaging is available, a local recurrence will be defined as an increase of $\geq$ 20% in tumor size.

2.3.2 Secondary endpoint will be late toxicity rate.

- Grading of acute and late complications is defined in Section 12.3 (Appendix III)

3.0 Patient Selection

3.1 Eligibility Criteria

3.1.1 Patient age of at least 18 years

3.1.2 Zubrod performance status of 0-3

3.1.3 Vertebral and/or paraspinal metastases, with or without prior surgery and/or fractionated radiotherapy

3.1.4 Benign extradural spine tumors such as chordomas, meningiomas, schwannomas, neurofibromas, paragangliomas, and arteriovenous malformations (AVMs).

3.1.5 Established histologic diagnosis of a benign or malignant tumor of the spine. For patients with malignant spine tumors, the histologic diagnosis may come from biopsy of the primary tumor site or an elsewhere metastatic site. If this represents the first appearance of metastatic disease, however, the diagnosis of metastasis should be histologically confirmed, when possible.

3.1.7 Arteriovenous malformation of the spine identified radiographically (no biopsy)

3.1.8 Well-defined lesion involving no more than 2 adjacent vertebral levels or spinal segment

3.1.9 No overt spinal instability

3.1.10 Neurologic deficit is unrelated to bony fragments/bony compression of neural structures

3.1.11 No previous radiation therapy at the involved level(s) within 3 months of radiosurgery

3.1.12 Minimal spinal canal compromise that is not rapidly progressive. Ideally, the tumor should not be within 5 mm of the spinal cord.

3.1.13 No pregnant or lactating women (negative serum pregnancy test for pre-menopausal women performed within 72 hours of registration)

3.1.14 If chemotherapy is planned, ideally it should not have been given within 30 days of starting radiation and should not resume until at least 2 weeks after completing radiation. In addition, it is not recommended to perform SBRT when targeted anti-angiogenesis therapy is planned within 2 months of the procedure.

3.1.15 Signed study-specific consent form

3.2 Exclusion Criteria

3.2.1 Lesion involving $\geq$ 3 adjacent vertebral levels

3.2.2 Overt spinal instability

3.2.3 Neurologic deficit due to bony fragments/bony compression of neural structures

3.2.4 Prior radiotherapy at the involved level(s) within 3 months of radiosurgery, more than one prior course of radiotherapy at the involved level(s), or more than 45 Gy previous radiation exposure at the involved level(s)

3.2.5 Rapidly progressive spinal cord compromise or neurological deficit

3.2.6 Paralysis, or otherwise compromised motor function due to radiographically confirmed cord compression

3.2.7 Patient unable to undergo an MRI

3.2.8 Pregnant or lactating women, due to potential exposure of the fetus to RT and unknown effects of RT on lactating females

3.2.9 Patients with psychiatric or addictive disorder that would preclude obtaining informed consent

4.0 Pretreatment Evaluation

4.1 Patient history, including prior radiation and chemotherapy treatments

4.2 Physical examination

4.3 Assessment of neurological function using the ASIA Impairment Score (Appendix IV)

4.4 Assessment of pain using a 10-point visual analogue scale (Appendix V)

4.5 Evaulation by an experience neurosurgeon that must include (1) an assessment of spinal stability, (2) an assessment of both medical and surgical operability

4.6 MRI of the affected spine

4.7 Tissue biopsy confirming a diagnosis of malignancy (may be at the primary site, another metastatic site, or the spinal metastatic site dependent on the clinical situation) in the case of metastatic tumors. Primary tumors should also be biopsy confirmed, except in the case of vascular malformations.

4.8 CBC, platelets, bilirubin, AST, ALT, alkaline phosphatase, renal panel within 1 month of planned radiosurgery, if clinically indicated

5.0 Simulation

5.1 Custom Mask and Bite Block Device, such as the HeadFix or Esarte frame, (for C-spine) or Body Fix (for TLS-spine) immobilization device

5.2 CT simulation without IV contrast with 1-2 mm slice thickness, including the treatment volume and at least 3 vertebral bodies above and below the target area. When necessary, the planning CT scan will be performed with intravenous contrast and/or oral contrast to aid in target and normal tissue definition.

5.3 3-point leveling tattoos

5.4 Contrast enhanced MRI with 1-3 mm slice thickness through the involved spine levels performed without the immobilization device, to allow for CT-MRI fusion for target volume and normal tissue delineation

6.0 Radiation Treatment Planning

6.1 Target Definition

6.1.1 Gross tumor volume (GTV) is contoured on the planning CT scan. MRI images will be registered to the planning CT dataset to assist in constructing the GTV.

6.1.2 Clinical target volume (CTV) will be equal to the GTV

6.1.3 Planning target volume (PTV) for vertebral metastases will be defined as the CTV plus a 2-5 mm margin, at the discretion of the treating radiation oncologist. It is recommended that consideration be given to including the entire involved vertebral body plus the pedicles and posterior elements of the involved vertebral bodies.

6.1.4 The PTV for benign tumors will be defined as the CTV plus a 2-5 mm margin, at the discretion of the treating radiation oncologist. The PTV may be modified to exclude the spinal cord and cauda equina volumes.

6.2 Normal Tissue Definition

6.2.1 Required normal tissue contours will vary according to the level of spinal irradiation and corresponding organs at risk. The spinal cord (including the cauda equina when appropriate) will be contoured for all cases. The esophagus, stomach, bowel, kidneys, liver, larynx, lungs, and heart will be contoured when appropriate.

6.2.2 Spinal cord – Contours should extend from the superior slice of the planning CT scan or the foramen magnum (whichever is most caudad) to the inferior slice of the planning CT scan or the terminal end of the spinal cord (whichever is most cephalad). The volume may be expanded by 1-2 mm for setup uncertainty.

6.2.3 Cauda Equina – Contours should extend from the superior slice of the planning CT scan or the terminal end of the spinal cord (whichever is most caudad) to the inferior slice of the planning CT scan or the terminal end of the cauda equina (which is most cephalad), and includes the entire thecal sac. The volume may be expanded by 1-2 mm for setup uncertainty.

6.2.4 Esophagus – Contours should include the entire esophagus, from 2 cm above the manubrium to the level of the gastroesophageal (GE) junction. When possible, oral contrast should be utilized to aid in volume definition.

6.2.5 Stomach – Contours should include the entire stomach, with the proximal limit at the GE junction. When possible, oral contrast should be utilized to aid in volume definition.

6.2.6 Bowel – Contours should include both small and large bowel. When possible, oral contrast should be utilized to aid in volume definition.

6.2.7 Kidneys – Contours should include the entire left and right kidneys, including the renal parenchama and adjacent proximal collecting system.

6.2.8 Liver – Contours should include the entire liver, from the hepatic dome to its inferior border.

6.2.9 Larynx – Contours should include the entire larynx, from the hyoid bone through the cricoid cartilage

6.2.10 Lungs – Contours should include the entire left lung, right lung, and both lungs.

6.2.11 Heart – Contours should include the entire heart along with the pericardial sac, from the upper limit of the right atrium and right ventricle (excluding the pulmonary trunk, ascending aorta, and SVC) to the inferior extent of the myocardium.

6.2.12 Skin – Contour should include a 5 mm thick volume beneath the skin surface.

6.3 Dose-Specification

6.3.1 Radiation beams will conform to the PTV outline without additional margin and the dose will be prescribed to the isodose line (IDL) that covers at least 95% of the PTV, which is typically around 80%.

6.3.2 SBRT dose-fractionation scheme will be chosen at the discretion of the treating radiation oncologist, but the normal tissue dose constraints must be maintained. Suggested dose-fractionation schemes, derived from the available literature, are listed below. Also included are the corresponding biologic equivalent dose (BED) for each based on the linear-quadratic model:

	SBRT scheme	*BED[1] (α/β=10)*	*BED[2] (α/β=3)*	*Equivalent 2 Gy/Fx Dose[1] (α/β=10)*	*Equivalent 2 Gy/Fx Dose[2] (α/β=3)*
Vertebral Metastases	25 Gy x 1	87.5 Gy	233.3 Gy	72.9 Gy	140 Gy
	24 Gy x 1	81.6 Gy	216 Gy	68 Gy	129.6 Gy
	23 Gy x 1	75.9 Gy	199.3 Gy	63.25 Gy	119.6 Gy
	22 Gy x 1	70.4 Gy	183.3 Gy	58.7 Gy	110 Gy
	21 Gy x 1	65.1 Gy	168 Gy	54.25 Gy	100.8 Gy
	20 Gy x 1	60 Gy	153.3 Gy	50 Gy	92 Gy
	19 Gy x 1	55.1 Gy	139.3 Gy	45.9 Gy	83.6 Gy
	18 Gy x 1	50.4 Gy	126 Gy	42 Gy	75.6 Gy
	17 Gy x 1	45.9 Gy	113.3 Gy	38.25 Gy	68 Gy
	16 Gy x 1	41.6 Gy	101.3 Gy	34.7 Gy	60.8 Gy
	15 Gy x 1	37.5 Gy	90 Gy	31.25 Gy	54 Gy
	14 Gy x 1	33.6 Gy	79.3 Gy	28 Gy	47.6 Gy
	9 Gy x 3	51.3 Gy	108 Gy	42.75 Gy	64.8 Gy
	8 Gy x 3	43.2 Gy	88 Gy	36 Gy	52.8 Gy
	7 Gy x 3	35.7 Gy	70 Gy	29.75 Gy	42 Gy
	6 Gy x 5	48 Gy	90 Gy	40 Gy	54 Gy
	5 Gy x 5	37.5 Gy	66.7 Gy	31.25 Gy	40 Gy
Intramedullary Spinal Metastases	5 Gy x 5	37.5 Gy	66.7 Gy	31.25 Gy	40 Gy
Benign Extradural Spine Tumors	16 Gy x 1	41.6 Gy	101.3 Gy	34.7 Gy	60.8 Gy
	15 Gy x 1	37.5 Gy	90 Gy	31.25 Gy	54 Gy
	14 Gy x 1	33.6 Gy	79.3 Gy	28 Gy	47.6 Gy
	13 Gy x 1	29.9 Gy	69.3 Gy	24.9 Gy	41.6 Gy
	12 Gy x 1	24.6 Gy	60 Gy	22 Gy	36 Gy
	9 Gy x 3	51.3 Gy	108 Gy	42.75 Gy	64.8 Gy
	8 Gy x 3	43.2 Gy	88 Gy	36 Gy	52.8 Gy
	7 Gy x 3	35.7 Gy	70 Gy	29.75 Gy	42 Gy
	6 Gy x 5	48 Gy	90 Gy	40 Gy	54 Gy
	5 Gy x 5	37.5 Gy	66.7 Gy	31.25 Gy	40 Gy

[1]Cancers are assumed to have an α/β ratio of approximately 10

[2]Normal tissues are assumed to have an α/β ratio of approximately 3

6.4 Normal Tissue Dose Constraints

6.4.1 Tissues arranged in series, where the function of each subunit is vital for organ function, include the gastrointestinal tract and spinal cord

6.4.1.1 Esophagus, Stomach

- Maximum point dose, $D_{max} \leq$ 15 Gy in 1 fraction ($\leq$ 1 cc to > 10 Gy)
- Maximum point dose, $D_{max} \leq$ 24 Gy in 3 fractions (8 Gy per fraction)
- Maximum point dose, $D_{max} \leq$ 30 Gy in 5 fractions (6 Gy per fraction)

6.4.1.2 Bowel
- Maximum point dose, $D_{max} \leq 15$ Gy in 1 fraction
- Maximum point dose, $D_{max} \leq 24$ Gy in 3 fractions (8 Gy per fraction)
- Maximum point dose, $D_{max} \leq 30$ Gy in 5 fractions (6 Gy per fraction)

6.4.1.3 Spinal Cord
- < 0.5 cc to 8 Gy in 1 fraction
- < 0.3 cc to 10 Gy in 1 fraction
- < 0.15 cc to 12 Gy in 1 fraction
- Maximum point dose, $D_{max} \leq 18$ Gy in 3 fractions (6 Gy per fraction)
- Maximum point dose, $D_{max} \leq 22.5$ Gy in 5 fractions (4.5 Gy per fraction)

6.4.1.4 Cauda Equina
- Maximum point dose, $D_{max} \leq 13$ Gy in 1 fraction
- Maximum point dose, $D_{max} \leq 21$ Gy in 5 fractions (7 Gy per fraction)
- Maximum point dose, $D_{max} \leq 25$ Gy in 5 fractions (5 Gy per fraction)

6.4.2 Tissues arranged in parallel includes the liver parenchyma, kidneys, skin, and lungs

6.4.2.1 Liver critical volume model
- Maximum point dose, $D_{max} \leq 15$ Gy in 1 fraction
- At least 700 cc of normal liver volume must receive < 15 Gy in 3 fractions (9.5 Gy in 1 fraction; 18 Gy in 5 fractions), which has a BED_{2Gy} (α/β=3) of 40 Gy (equivalent to 24 Gy in 2 Gy fractions)
- At least 35% of normal liver must receive < 15 Gy in 3 fractions

6.4.2.2 Kidneys
- mean dose $\leq$ 3 Gy
- $V_{10} \leq 10\%$

6.4.2.3 Skin
- Maximum point dose, $D_{max} \leq 15$ Gy in 1 fraction
- Maximum point dose, $D_{max} \leq 24$ Gy in 3 fractions (8 Gy per fraction)
- Maximum point dose, $D_{max} \leq 30$ Gy in 5 fractions (6 Gy per fraction)

6.4.2.4 Lungs
- $\leq$ 10% of total lung volume receiving $\geq$ 20 Gy (V_{20})
- $\leq$ 40% of total lung volume receiving $\geq$ 5 Gy (V_5)

7.0 Stereotactic Body Radiotherapy Treatment Delivery

7.1 Premedication

The decision to premedicate a patient prior to spine SBRT is at the discretion of the radiation oncologist and/or neurosurgeon. While there is no universal agreement, the following are a list of agents that have been suggested by some investigators to potentially reduce patient discomfort, and possibly prevent acute and/or late toxicity if used as premedication prior to spine SBRT.

7.1.1 Corticosteroids (Decadron 4-10 mg PO or equivalent) 15-60 minutes prior to each fraction for the intended purpose of modulating immediate inflammatory effects.

7.1.2 Analgesic premedication to avoid general discomfort during long treatment durations.

7.1.3 Prophylactic antiemetics (Zofran 4-8 mg PO or Kytril 2 mg PO) 45-60 minutes prior to each fraction to possibly prevent acute nausea

7.1.4 Anti-anxiety medication for patient comfort during long treatment duration

7.2 Treatment

7.2.1 The medical physics staff will perform routine quality assurance checks on the treatment machine to ensure that the mechanical isocenter stability is within specification (ie. diameter $\leq$ 1.5 mm).

7.2.2 The medical physics staff will perform patient-specific quality assurance measurements to ensure that the treatment plan is deliverable and that the dose distribution is accurate.

7.2.3 The patient will be positioned in the custom immobilization device on the Hexapod® treatment couch and aligned to 3-point setup points with the in-room lasers.

7.2.4 Daily CT localization of the GTV isocenter is required prior to each fraction. Once the patient is properly positioned, a cone-beam CT of the treatment area is acquired, fused, and aligned to the treatment planning CT. Translational and rotational adjustments of patient positioning are performed as indicated. If adjustments are required, an orthogonal (ex. AP and LATERAL) set of electron portal images or a second cone-beam CT of the treatment area will be obtained prior to treatment to confirm proper alignment of the isocenter. A third cone-beam CT may be obtained following treatment delivery to assess for intra-fraction motion. Depending on the overall treatment time, an additional cone-beam CT scan may be obtained during treatment at the discretion of the treating radiation oncologist to ensure accuracy of the isocenter alignment and target localization.

7.2.5 Either multiple coplanar or noncoplanar static gantry angle intensity-modulated fields or rotational arcs will be utilized.

7.2.6 Only photon (x-ray) beams will be used, preferably in energies of 6-18 MV.

8.0 Drug Therapy

8.1 The use of chemotherapy is left to the discretion of the medical oncologist.

8.2 Chemotherapy agents during radiation is not allowed. Ideally, chemotherapy should not have been given within 30 days of starting radiation and should not resume until at least 2 weeks after completing radiation. In addition, it is not recommended to perform SBRT when targeted anti-angiogenesis therapy is planned within 2 months of the procedure.

9.0 Patient Assessment

9.1 Study Parameters

The following are suggested patient follow-up intervals and evaluations that may be performed to either assess for treatment toxicity or tumor response to SBRT:

Assessment	Pre-Rx	Post-Rx 6 wk	Post-Rx 3 mo	Post-Rx 6 mo	Post-Rx 9 mo	Post-Rx 1 yr
H&P / Weight	X	X	X	X	X	X[b]
Disease status	X	X	X	X	X	X[b]
Neurologic Function	X	X	X	X	X	X[b]
Pain Score	X	X	X	X	X	X[b]
Toxicity Assessment		X	X	X	X	X[b]
AST / ALT / Alk Phos	X[a]					
Total Bilirubin	X[a]					
Creatinine	X[a]					
CBC with Platelets	X					
Pregnancy test	X[a]					
MRI of affected spine	X	X[c]	X[c]	X[c]	X[c]	X[c]
PET/CT	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]

a if clinically appropriate

b clinical examination, neurologic function, pain score, late toxicity, and disease status assessment at 3 month intervals for first year, then at the discretion of the treating radiation oncologist

c at the discretion of the treating radiation oncologist

9.2 Response Evaluation

9.2.1 It is recognized that many patients will not undergo follow-up imaging. Evaluation of treatment response in these patients will be clinical.

- Local recurrence will be defined as worsening or no improvement in pain or neurologic compromise.

9.2.2 MRI scan of the affected spine with IV contrast

- Local recurrence will be defined as tumor recurrence or progression within the planning target volume with an increase of $\geq$ 20% in tumor size.

9.2.3 PET/CT scan

- May be obtained at the discretion of the treating radiation oncologist if there is uncertainty on the diagnostic MRI scan as to the disease status

9.3 Toxicity

9.3.1 The investigator will report and record all serious adverse events that occur. Adverse events should be reported using the CTC grading system (Appendix III).

9.3.2 Examples of anticipated acute adverse events include:

- General malaise
- Nausea occurring within a few hours of treatment
- Anorexia
- Radiation dermatitis – dryness, tanning, redness, itching
- Localized hair loss
- Musculoskeletal pain
- Dysphagia / Esophagitis
- Hoarseness
- Pneumonitis
- Diarrhea
- Neurologic changes including motor weakness, numbness, and/or paresthesias

9.3.3 Examples of anticipated late adverse events include:

- Myelopathy resulting in motor weakness, numbness, and/or paresthesias
- Vertebral body collapse
- Persistent dysphagia, or esophageal stricture
- GI toxicity may consist of bleeding, ulceration and/or perforation of the esophagus, stomach, duodenum, or bowel.
- Impaired liver function
- Reduction in kidney function
- Reduction in lung function
- Decrease in thyroid function
- Persistent hoarseness
- Localized skin fibrosis, edema, and/or ulceration
- Radiation-induced secondary malignancy

9.3.4 Reporting of unanticipated or serious adverse events will be reported according to the institutions IRB policy. An unanticipated adverse effect is defined as follows:

> Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, stereotactic body radiotherapy, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a treatment that relates to the rights, safety, or welfare of subjects.

9.4 Patient Withdrawal from Study

During the course of the study, it is possible that patients may withdraw or be withdrawn from the study. Factors that may lead to a withdrawal from the study may include, but are not limited to the following:

Patient Withdrawal……At any time a patient may voluntarily withdraw from the study. This withdrawal will not affect their future medical treatment or benefits.

Patient Lost to Follow-Up…….Should a patient be classified as lost to follow-up, efforts to contact the patient should be made.

Physician Decision……Should a physician decide that continuing in the study is detrimental to the health and welfare of the patient, the patient may be withdrawn from the study.

Medical Reason…….Should the patient condition deteriorate the patient may be withdrawn from the study to allow for proper medical care.

10.0 Risk/Benefit Analysis

10.1 Risk associated with SBRT for spine metastases and primary spine tumors

10.1.1 Acute toxicities reported to occur as a result of SBRT for spine metastases and benign spine tumors include, but are not limited to: general malaise, nausea, anorexia, radiation dermatitis, local hair loss, local musculoskeletal pain, dysphagia/esophagitis, hoarseness, diarrhea, and neurologic changes including motor weakness, numbness, and/or paresthesias

10.1.2 Late toxicities reported to occur as a result of SBRT for spine metastases and benign spine tumors are uncommon and primarily neurologic, consisting of motor weakness, numbness, and/or paresthesias. Other serious late toxicities are rare and may include vertebral body collapse, persistent dysphagia, esophageal stricture, bowel ulceration and/or perforation, impaired liver function, reduction in kidney function, reduction in lung function, hypothyroidism, persistent hoarseness, and localized skin fibrosis edema and/or ulceration.

10.2 Minimization of Risks

Although the risks outlined in Section 9.3 may occur, the likelihood of serious events occurring is considered uncommon as long as certain precautions are taken. The potential risks have been minimized by:

- Premedication as described in Section 7.1
- Strict compliance with normal tissue dose constraints as described in Sections 6.4

10.3 Potential Patient Benefits

10.3.1 Ability to offer effective and expedient local therapy to patients with limited life expectancy from spine metastases

10.3.2 Reduction in amount of radiation delivered to adjacent normal structures compared to standard-fractionation radiation therapy

10.3.3 Reduced treatment duration compared to standard-fractionation radiation therapy

10.3.4 Ability to avoid surgery potentially associated with significant risk of morbidity

10.4 Justification of the Study

Patients who have spine metastases are not curable and often have a limited life expectancy. Local tumor control is important for prevention of tumor-related pain, pathologic fractures, and neurologic deterioration due to spinal cord / cauda equina compression. Standard fractionation radiation therapy consists of a daily treatment regimen for approximately 2-3

weeks, and has demonstrated unsatisfactory complete pain relief rates and tumor control rates. Stereotactic body radiotherapy shortens the radiation course to only 1-5 sessions. Non-surgical treatment for recurrent spine metastases is very limited. Traditional radiation therapy cannot be repeated at the same site in the spine, due to the increased risk of injury to normal tissue. Spinal surgery is often difficult and can be associated with significant risk, or may not be an option due to prior surgery, other medical conditions or limited life expectancy. Stereotactic body radiotherapy offers an alternative to surgery for management of recurrent disease. Recent phase I/II trials of SBRT for spine metastases have reported local tumor control rates of 81-95%, durable improvement in pain of 67-100%, and improvement in neurologic function of 84%, with low toxicity rates. Surgical management of patients with benign spine tumors can be associated with significant risk of morbidity. The advantage of stereotactic body radiotherapy is that it is not painful, and does not require anesthesia or hospitalization.

10.5 Statistical Analysis

10.5.1 The overall survival and local control rates will be analyzed.

10.5.2 The incidence rate for any serious adverse events will be calculated.

11.0 References

(1) Chow E. *Palliative radiotherapy trials for bone metastases: A systematic review*. J Clin Oncol. 25:1423-1436, 2007.

(2) Potters L. *American Society for Therapeutic Radiology and Oncology and American College of Radiology practice guidelines for the performance of stereotactic body radiation therapy.* Int J Radiat Oncol Biol Phys. 60:1026-1032, 2004.

(3) Sahgal A. *Stereotactic body radiosurgery for spinal metastases: A critical review*. Int J Radiat Oncol Biol Phys. 71(3):652-665, 2008.

(4) Gerszten PC. *Radiosurgery for spinal metastases: Clinical experience in 500 cases from a single institution.* Spine 32:193-199, 2007.

(5) Gerszten PC. *Stereotactic radiosurgery for spinal metastases from renal cell carcinoma.* J Neurosurg Spine. 3:288-295, 2005.

(6) Gerszten PC. *Radiosurgery for the treatment of spinal melanoma metastases.* Stereotac Func Neurosurg. 83:213-221, 2005.

(7) Chang EL. *Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure.* J Neurosurg Spine 7:151-160, 2007.

(8) Yamada PC. *High-dose single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions*. Int J Radiat Oncol Biol Phys. 71(2):484-490, 2008.

(9) Gibbs IC. *Spinal and paraspinal lesions: The role of stereotactic body radiotherapy*. Fron Radiat Ther Oncol 40: 407-414, 2007

(10) Dodd RL. *CyberKnife radiosurgery for benign intradural extramedullary spinal tumors*. Neurosurgery 58:674-685, 2006.

12.0 Appendices

12.1 Appendix I

St. John's Mercy Medical Center
Informed Consent for a Clinical Research Study

STUDY TITLE: PHASE IV TRIAL EVALUATING THE USE OF STEREOTACTIC BODY RADIOTHERAPY FOR THE TREATMENT OF SPINE METASTASES AND PRIMARY SPINE TUMORS

This is a clinical trial (type of research study). Clinical trials include only patients who choose to take part. This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family and friends before making your decision.

WHAT SHOULD YOU KNOW ABOUT THE RESEARCH DOCTOR?

You should know that your relationship with a research doctor is different from your relationship with your personal doctor. Your personal doctor is treating your specific problem with the hope of a benefit for you. When a doctor is your research doctor, he/she is treating all subjects under a specific protocol to learn about the results of a treatment, and with the understanding that you may or may not benefit from your participation in the study. Be sure to ask questions of the study doctor if you want more information about this relationship.

WHY IS THIS STUDY BEING PERFORMED?

Treatment of cancer that has spread to the spine (metastases) and tumors that begin in the spine (primary tumors) is challenging and the outcome is often disappointing. Treatment may consist of surgery, radiation therapy, or a combination of surgery followed by radiation therapy. Radiation therapy has been used to improve local tumor control, alleviate tumor-related pain, prevent spine fractures, and improve neurologic symptoms such as weakness and numbness. Spinal surgery is often difficult and can be associated with significant risk, or may not be an option due to prior surgery or other medical conditions. While a standard course of radiation therapy may take 2-6 weeks of daily treatment to complete, recent technological advancements allow high-dose precisely targeted radiation treatment to be delivered in only 1-5 sessions. This technique is called stereotactic body radiotherapy. The advantage of stereotactic radiotherapy over surgery is that it is not painful, and does not require anesthesia or hospitalization. Several institutions have reported excellent local tumor control, pain relief, and neurologic improvement, with low toxicity risk. The purpose of this study is to collect additional data on the effectiveness of stereotactic body radiotherapy for spine metastases and primary spine tumors.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately 50 people are expected to participate in this clinical study.

WHAT IS INVOLVED IN THE STUDY?

If you wish to take part in this study, a series of tests will be performed to determine if you qualify for participation in the clinical study. Your physician will ask you a series of questions regarding your

medical history and a standard physical exam will be performed. If you are a woman of childbearing age, you may be asked to give a urine or blood specimen so that a pregnancy test can be performed.

If you qualify for the study, you will undergo a radiation treatment planning session called a simulation. At this visit, a custom rigid foam device will be fabricated to immobilize your body in the correct position for treatment. A CT scan and an MRI scan will be obtained to plan your treatment. Permanent small tattoos may be applied to your skin to aid in positioning your body on the treatment table.

There may be several days between the simulation and the day you begin radiation. During this time, complex radiation treatment planning will be performed by your radiation oncologist and their medical physics staff. You will receive between 1-5 radiation treatments. Your physician will explain your treatment in more detail. Each radiation session may take an hour or longer to complete. After the entire radiation course is complete, you will be given follow-up instructions.

HOW LONG WILL I BE IN THE STUDY?

We anticipate that you will remain in the study for approximately 5 years. After treatment is completed routine follow-up visits will be conducted, typically at 3 month intervals for the first year, then less frequently.

Your physician may decide stop your treatment if: 1) your disease becomes worse, or 2) side effects become very severe, or 3) new scientific developments occur that indicate the treatment is not in your best interest, or 4) your physician believes that this treatment is no longer in your best interest. If your treatment is stopped, your doctor will discuss further treatment options with you.

WHAT ARE THE RISKS OF THE STUDY?

By participating in this study, you are at risk for several possible expected and unexpected side effects associated with stereotactic body radiotherapy to the spine. Some of these are described below; however, there also may be other side effects that we cannot predict. Most side effects go away shortly after the radiation therapy is stopped, but in some cases side effects can be serious, long-lasting, or permanent.

Risks arising from the delivery of stereotactic radiotherapy to the spine which may occur shortly after completing treatment may include, but are not limited to:

- Fatigue
- Nausea occurring within a few hours of treatment
- Loss of appetite
- Hair loss over the treatment area
- Skin redness over the treatment area
- Skin tanning over the treatment area
- Dry peeling of skin over the treatment area
- Moist desquamation over the treatment area
- Dry itchy skin
- Muscular pain over the treatment area
- Dysphagia (difficulty swallowing)
- Dyspnea (shortness of breath)
- Hoarseness
- Diarrhea
- Neurologic changes including motor weakness, numbness, and/or paresthesias

Risks arising from the delivery of stereotactic radiotherapy to the spine which may develop several months to years after completing treatment may include, but are not limited to:

- Bleeding ulceration and/or perforation (hole) in the stomach, duodenum, and/or small bowel
- Scarring, swelling, and/or ulceration of the skin over the treatment area
- Persistent dysphagia (difficulty swallowing) or esophageal stricture
- Persistent hoarseness
- Decrease in liver function
- Decrease in kidney function
- Dyspnea (shortness of breath) due to decrease in lung function
- Decrease in thyroid function
- Vertebral body collapse / fracture
- Neurologic changes including motor weakness, numbness, and/or paresthesias

I understand that all these side effects are possible. I may experience no side effects, some of them, or most of them. Although I will be closely monitored, not all side effects can be predicated and unforeseen problems can arise. I understand that there may be some unknown or unanticipated risks or discomforts in addition to those specified here.

Reproductive risks: Because even very small doses of radiation can affect an unborn baby, you should not become pregnant while receiving radiation treatment. You should also not nurse a baby while receiving radiation treatment.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be a direct medical benefit to you. However, there have been several trials completed at other institutions that have shown high local control rates, improvement in pain and neurologic symptoms after stereotactic body radiotherapy for spine metastases and primary spine tumors. It is also convenient, requiring only 1-5 radiation sessions and no anesthesia or hospitalization. Toxicity risk has been reported to be fairly low.

WHAT OTHER OPTIONS ARE THERE?

Other treatment options may include surgery, chemotherapy, standard-fractionation radiation therapy, or other investigational procedures or medications. Another option is no further therapy. Your doctor can provide information about your disease and the benefits of the different treatments for you. You should feel free to talk with your doctor about your disease and expected outcomes. The doctor involved in your care will be available to answer any questions you have about this program. You are free to ask your doctor any questions concerning this program now or in the future.

You are free to seek care from a doctor of your choice at any time. If you do not take part in, or withdraw from, the study you will continue to receive alternate care.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. This Informed Consent and another document called an "Authorization to Use and Disclose Health Information" control how your health information may be used and disclosed during and after this study. The results of this study may be published or presented at meetings but will not include your name or reveal your identity. To participate in this study, you must sign both the Informed Consent and the Authorization to Use and Disclose Health Information. Your personal information may be disclosed if required by law.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance carrier. Specifically, you or your insurance carrier will be responsible for the costs of the baseline blood tests, diagnostic imaging studies, stereotactic radiotherapy planning and delivery, and follow-up visits which would otherwise be a standard part of your care. Please ask about any expected added costs or insurance problems. St. John's Mercy Medical Center has personnel that can assist you with this.

Every precaution will be taken to prevent any injury to you during the study. In the event that injury occurs as a result of this study, treatment will be available. You or your insurance carrier will be responsible for the costs of the treatment. No funds have been set aside for compensation in the event of a research related injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. You will not receive payment for participating in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Your participation is voluntary. You may choose not to take part or may leave the study at any time. Your choice will not affect your doctors from providing care to you. Choosing not to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled.

You will be told of any important new findings developed during the course of your participation in this study that may affect your willingness to continue in the study. The investigator may withdraw you from this study if issues occur that show that you should not continue to participate.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions or concerns regarding this study, or a research-related injury, you may contact one of the Principal Investigators, Dr. Julie Mai at 314-251-6844 or Dr. Bethany Sleckman at 314-251-6770.

For questions about your rights as a research participant, contact Dr. Donald York, Chairman of the St. John's Mercy Medical Center Institutional Review Board (which is a group of people who review the research to protect your rights), at 314-569-6453.

Your doctor understands the importance of your contribution to clinical studies that attempt to improve medical care. Your doctor will make every effort to minimize, control, and treat any problems that may happen as a result of your participation in this study. If you believe that you are injured solely as a result of the study, or if you have questions regarding the study, please contact the Principal Investigator.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at 1-800-422-6237 or TTY:1-800-322-8615

Visit the NCI's Web Sites:

- Cancer Trials: comprehensive clinical trials information
  http://cancertrials.nci.nih.gov
- CancerNet: accurate cancer information including PDQ
  http://cancernet.nci.nih.gov

SIGNATURES

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion. I willingly give my consent to participate in this study. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

Participant (sign) _____

Participant (written) _____

Date _____

Principal Investigator _____

Staff Member Performing Consent Process _____

Witness _____

IRB Stamp (This form is INVALID if the stamp is not present.)

12.2 Appendix II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all pre-disease activities without restriction (KPS 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (KPS 70-80)
2	Ambulatory and capable or all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (KPS 50-60)
3	Capable of only limited self-care, confined to bed or chair 50% of more of waking hours (KPS 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (KPS 10-20)

12.3 Appendix III

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

	GRADE				
Toxicity	**1**	**2**	**3**	**4**	**5**
CONSTITUTIONAL					
Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	-
Fever	100.4-102.2°F	102.3-104.0°F	> 104.0°F for ≤ 24 hr	> 104.0°F for > 24 hr	Death
Weight loss	5 - < 10% of baseline	10 - < 20% of baseline	≥ 20% of baseline; tube feeding or TPN indicated	-	-
PAIN					
Pain due to radiation	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	-
Myositis (inflammation or damage of muscle)	Mild pain not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
SKIN					
Radiation dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other that skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	
Telangiectasia	Few	Moderate number	Many and confluent	-	-
Ulceration	-	Superficial ulceration < 2 cm size; local wound care; medical intervention indicated	Ulceration ≥ 2 cm size; operative debridement, primary closure or other invasive intervention indicated (ex. Hyperbaric oxygen)	Life-threatening consequences; major invasive intervention (ex. Complete resection, tissue reconstruction, flap, grafting)	Death
Fibrosis	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disability; loss of limb; interfering with vital organ function	Death
Soft Tissue Necrosis	-	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (ex. Hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (ex. Tissue reconstruction, flap, or grafting)	Death
NEUROLOGY					
Neuropathy: Motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated	Life-threatening; disabling (e.g. paralysis)	Death
Neuropathy: Sensory	Asymptomatic, lost deep tendon reflexes or paresthesia (including tingling), not interfering with function	Symptomatic alteration or paresthesia (including tingling), interfering with function, not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death

ENDOCRINE					
Thyroid function, low (hypothyroidism)	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
PULMONARY/UPPER RESPIRATORY					
Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
Voice changes/ Dysarthria (e.g. hoarseness, loss or alteration in voice, laryngitis)	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes, including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g. electrolarynx) for $\leq$ 50% communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g. electrolarynx) for > 50% communication or requires > 50% written communication	Death
Pneumonitis/ Pulmonary infiltrates	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
Pulmonary fibrosis	Minimal radiographic findings (or patchy or bibasilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of < 25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 - <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50% - <75%	Estimated radiographic proportion of total lung volume that is fibrotic of $\geq$ 75%	Death
GI TRACT					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition; IV fluids indicated < 24 hr	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated $\geq$ 24 hr	Life-threatening consequences	Death
Vomiting	1 episode in 24 hr	2-5 episodes in 24 hr; IV fluids indicated < 24 hr	$\geq$ 6 episodes in 24 hr; IV fluids or TPN indicated $\geq$ 24 hr	Life-threatening consequences	Death
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of $\geq$ 7 stools per day over baseline; IV fluids indicated $\geq$ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucous or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (ex. Perforation, bleeding, ischemia, necrosis)	Death
Esophagitis	Asymptomatic, pathologic, radiographic or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g. altered dietary habits, oral supplements); IV fluids indicated < 24 hrs	Symptomatic and severely altered eating/swallowing (e.g. inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated $\geq$ 24 hrs	Life-threatening consequences	Death

Ulceration	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (altered dietary habits, oral supplements); IV fluids indicated < 24 hr	Symptomatic and severely altered GI function (inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 hr	Life-threatening consequences	Death
Bleeding	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
Perforation	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated < 24 hr	IV fluids, tube feedings, or TPN indicated ≥ 24 hr; operative intervention indicated	Life-threatening consequences	Death
Stricture	Asymptomatic radiographic findings only	Symptomatic; altered GI function (altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated < 24 hr	Symptomatic and severely altered GI function (altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥ 24 hr; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection	Death
Fistula	Asymptomatic; radiographic findings only	Symptomatic; altered GI function (ex. Altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated < 24 hr	Symptomatic and severely altered GI function (ex. Altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥ 24 hr	Life-threatening consequences	Death
MUSCULOSKELETAL					
Fracture	Asymptomatic, radiographic findings only	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced; operative intervention indicated	Disabling	Death
HEPATOBILIARY					
Liver Dysfunction	-	Jaundice	Asterixis	Encephalopathy or come	Death
RENAL					
Renal failure	-	-	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
METABOLIC					
Albumin	3-4 g/dL	2-2.99 g/dL	< 2 g/dL		Death
Alkaline phosphatase	> nl – 2.5 x nl	> 2.5 – 5 x nl	> 5 – 20 x nl	> 20 x nl	-
ALT	> nl – 2.5 x nl	> 2.5 – 5 x nl	> 5 – 20 x nl	> 20 x nl	-
AST	> nl – 2.5 x nl	> 2.5 – 5 x nl	> 5 – 20 x nl	> 20 x nl	-
Bilirubin	> nl – 1.5 x nl	> 1.5 – 3 x nl	> 3 – 10 x nl	> 10 x nl	-
Creatinine	> nl – 1.5 x nl	> 1.5 – 3 x nl	> 3 – 6 x nl	> 6 x nl	Death
SECONDARY MALIGNANCY	-	-	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia, or lymphoma	Death

12.4 Appendix IV

ASIA Impairment Scale

A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5
B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade of less than 3
D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more
E	Normal	Motor and sensory function are normal

Muscle Grading

0	Total paralysis
1	Palpable or visible contraction
2	Active movement, full range of motion, gravity eliminated
3	Active movement, full range of motion, against gravity
4	Active movement, full range of motion, against gravity and provides some resistance
5	Active movement, full range of motion, against gravity and provides normal resistance
5*	Muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present
NT	Not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture

12.5 Appendix V

10-point Visual Analog Pain Scale

12.6 Appendix VI

DEMOGRAPHIC FORM – Page 1 of 1

1. Name _____(last) _____(first)

2. Date of Birth ____/____/_____

3. RT Number _____

4. Race: ☐ Asian ☐ Caucasian ☐ Black ☐ Other, specify _____

5. Zubrod PS: ☐ 0 ☐ 1 ☐ 2

6. Radiation oncologist: _____

7. Medical oncologist: _____

8. Surgeon: _____

9. Tumor category: ☐ Metastases, specify location (cervical, thoracic, lumbosacral) _____
   Primary Site: ☐ Prostate cancer
   ☐ Breast cancer
   ☐ Lung cancer
   ☐ Colorectal cancer
   ☐ Renal cancer
   ☐ Melanoma
   ☐ Other, specify _____
   ☐ Primary spine tumor, specify histology _____

10. Maximum tumor diameter: _____ cm

11. Location of extraspinal disease: ☐ No gross extraspinal disease
    ☐ Stable extraspinal diasease
    ☐ Progressive extraspinal diasease

12. Baseline Labs (if clinically indicated):

Total bilirubin _____	ALT _____	AST _____
Alkaline phosphatase _____	PT _____	PTT _____
Creatinine _____		
WBC _____	Hb _____	Platelets _____

13. Baseline neurologic function using the ASIA Impairment Score: _____

14. Baseline assessment of pain using a 10-point visual analog scale: _____

15. Amount and type of narcotic analgesic usage: _____

16. Prior in-field spine radiation: ☐ No ☐ Yes, explain _____

17. Pre-SBRT chemotherapy: ☐ No
    ☐ Yes, regimen & last cycle date _____

Person completing form : Signature _____ Print Name _____

12.7 Appendix VII

TREATMENT FORM – Page 1 of 1

1. Name _____(last) _____(first)

2. RT Number _____

3. Tumor Details:

☐ Metastases, specify location (cervical, thoracic, lumbosacral) _____

Primary Site: ☐ Prostate cancer
☐ Breast cancer
☐ Lung cancer
☐ Colorectal cancer
☐ Renal cancer
☐ Melanoma
☐ Other, specify _____

Number of Vertebral Levels Involved: ☐ One
☐ Two

☐ Primary spine tumor, specify histology _____

Maximum Diameter (cm)	GTV Volume (cc)	PTV Margin (mm)			PTV Volume (cc)
		AP	R-L	C-C	

5. Treatment Portal Design:

☐ Static gantry angle (coplanar), specify number of fields _____
☐ Static gantry angle (non-coplanar), specify number of fields _____
☐ Dynamic arc (coplanar), specify number of arcs _____
☐ Dynamic arc (non-coplanar), specify number of arcs _____

6. Dose-Fractionation Scheme:

Total Dose (Gy)	Dose per Fraction (Gy)	# of Fractions	Prescription IDL (%)	D_{max} (Gy)	$BED_{\alpha/\beta=10}$ (Gy)	$BED_{\alpha/\beta=3}$ (Gy)	C.I.

7. Dose to Normal Tissues:

Spinal Cord: maximum dose _____ in _____ fractions
_____ cc to > 8 Gy in 1 fraction
_____ cc to > 10 Gy in 1 fraction
_____ cc to > 12 Gy in 1 fraction

Cauda Equina: maximum dose _____ in _____ fractions

Liver: _____ cc of normal liver volume received < BED $_{2Gy\ (\alpha/\beta=3)}$ of 40 Gy
_____ % of normal liver volume received < BED $_{2Gy\ (\alpha/\beta=3)}$ of 40 Gy
(9.5 Gy in 1 fraction; 15 Gy in 3 fractions; 18 Gy in 5 fractions)

Kidneys: mean right kidney dose of _____
mean left kidney dose of _____
V_{10} right kidney _____
V_{10} left kidney _____

Lung, Right: mean dose _____
V_5 _____
V_{10} _____
V_{20} _____

Lung, Left: mean dose _____
V_5 _____
V_{10} _____
V_{20} _____

Normal Tissue	D_{max} (Gy)
Esophagus	
Stomach	
Bowel	
Larynx	
Skin	

7. Premedication:
☐ None
☐ Anti-nausea, specify drug _____, dose _____ mg,
☐ Decadron, specify dose _____ mg
☐ Analgesics, specify drug _____, dose _____ mg

Person completing form : Signature _____ Print Name _____

12.8 Appendix VIII

FOLLOW-UP VISIT FORM – Page 1 of 2

1. Name _____(last) _____(first)

2. RT Number _____

3. Date of Visit: ____/____/_____

4. Blood work:

Lab		Date:		Date:		Date:	
Total Bilirubin							
Alkaline Phosphatase							
ALT	AST						
PT	PTT						
Creatinine							
WBC							
Hb							
Platelets							

4. Radiation Therapy related adverse events

Adverse Event	CTC V3.0 Grade	Timing	Treatment	Comments
ACUTE				
☐ Fatigue				
☐ Nausea				
☐ Vomiting				
☐ Loss of appetite				
☐ Weight loss				
☐ Enteritis				
☐ Diarrhea				
☐ Alopecia				
☐ Radiation dermatitis				
☐ Esophagitis				
☐ Hoarseness				
☐ Pneumonitis				
☐ Musculoskeletal Pain				
☐ Neuropathy, Motor				
☐ Neuropathy, Sensory				
LATE				
☐ GI Bleeding				
☐ GI Ulceration				
☐ GI Perforation				
☐ GI Stricture				
☐ Fistula				
☐ Liver Dysfunction				
☐ Kidney Dysfunction				
☐ Hoarseness				
☐ Pulmonary Fibrosis				
☐ Neuropathy, Motor				
☐ Neuropathy, Sensory				
☐ Thyroid Dysfunction				

☐ Vertebral Fracture				
☐ Telangiectasia				
☐ Skin Ulceration				
☐ Skin/SubQ Tissue Fibrosis				
☐ Soft Tissue Necrosis				
☐ Radiation-induced Malignancy				

5. Serious adverse event? ☐ No ☐ Yes, submit report to HIC

6. Has systemic therapy been given? ☐ No ☐ Yes

If yes, list therapy

Agent(s)	Start Date	Stop Date
_____	____/____/_____	____/____/_____
_____	____/____/_____	____/____/_____
_____	____/____/_____	____/____/_____

7. Neurologic function assessment using the ASIA Impairment Score: _____

8. Pain assessment using a 10-point visual analog scale: _____

9. Amount and type of narcotic analgesic usage: _____

10. MRI scan of the involved spine since last follow-up visit? ☐ No ☐ Yes, date ____ / ____ / _____

Tumor Response: ☐ Complete response
☐ Partial response
☐ Stable disease
☐ Progressive disease

11. PET/CT scan since last follow-up visit? ☐ No ☐ Yes, date ____ / ____ / _____

Tumor Response: ☐ Complete response
☐ Partial response
☐ Stable disease
☐ Progressive disease

12. Disease Status

	Date of Diagnosis
☐ No evidence of tumor	
☐ Local recurrence within the treatment volume	____/____/_____
☐ Distant recurrence, specify site _____	____/____/_____

12. Additional treatment for recurrent disease

Surgery	☐ Yes ☐ No	Date of surgery ____/____/_____
Chemotherapy, agents _____	☐ Yes ☐ No	Start date ____/____/_____
Other, specify _____	☐ Yes ☐ No	Start date ____/____/_____

13. Death? ☐ No ☐ Yes, date ____/____/_____ Cause? _____

Person completing form : Signature _____ Print Name _____