NRG ONCOLOGY

RTOG 0631

PHASE II/III STUDY OF IMAGE-GUIDED RADIOSURGERY/SBRT FOR LOCALIZED SPINE METASTASIS

Study Chairs (4/14/15)

Principal Investigator/Radiation Oncology
Samuel Ryu, MD
Department of Radiation Oncology
Stony Brook University School of Medicine
101 Nicolls Road
Stony Brook, NY 11794-7028
631-444-7770/FAX 631-444-6034
samuel.ryu@stonybrookmedicine.edu

Neurosurgery Co-Chair
Peter Gerszten, MD, MPH
University of Pittsburgh Medical Center
200 Lothrop Street, Suite A-402
Pittsburgh, PA 15213
412-647-0958/FAX 412-647-0989
gersztenpc@upmc.edu

Medical Physics Co-Chair
Fang-Fang Yin, PhD
Duke University Medical Center
Box 3295
Durham, NC 27710
919-660-2185/FAX 919-681-7183
fangfang.yin@duke.edu

Radiation Oncology/IGRT Co-Chair
Robert D. Timmerman, MD
University of Texas Southwestern
5801 Forest Park Road, NF3.302B
Dallas, TX 75390-9183
214-645-7651/ FAX 214-645-7622
Robert.Timmerman@UTSouthwestern.edu

Translational Research Co-Chair
Adam Dicker, MD, PhD
Thomas Jefferson University
111 S. 11th Street
Philadelphia, PA 19107
215-955-627/FAX 215-955-0412
adamdicker18@gmail.com

Quality of Life Co-Chair
Benjamin Movsas, MD
Henry Ford Health System
2799 W. Grand Blvd.
Detroit, MI 48202
313-916-5188/FAX 313-916-3235
bmovsas1@hfhs.org

Senior Statistician
Stephanie Pugh, PhD
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19013
215-574-0850/FAX 215-928-0153
pughs@nrgoncology.org

PHASE II/III STUDY OF IMAGE-GUIDED RADIOSURGERY/SBRT FOR LOCALIZED SPINE METASTASIS

Document History

	Version/Update Date	Broadcast Date
Closure with Amendment 10	**September 23, 2016**	**August 4, 2017**
Amendment 10	**September 23, 2016**	**October 31, 2016**
Amendment 9	August 14, 2015	August 24, 2015
Amendment 8	April 14, 2015	May 11, 2015
Update	June 27, 2014	June 27, 2014
Amendment 7	April 21, 2014	May 13, 2014
Update	11/22/2013	11/22/2013
Amendment 6	May 6, 2013	May 16, 2013
Amendment 5	May 1, 2012	May 3, 2012
Amendment 4	August 30, 2011	September 22, 2011
Amendment 3	March 18, 2011	May 19, 2011
Amendment 2	March 11, 2010	March 23, 2010
Update	December 1, 2009	December 1, 2009
Amendment 1	November 6, 2009	November 19, 2009
Update	August 11, 2009	August 11, 2009
Update	August 7, 2009	August 7, 2009
Activation	July 20, 2009	August 7, 2009

Participating Sites (5/6/13)
☐ U.S. Only
☐ Canada Only
☒ U.S. and Canada
☒ Approved International Member Sites

NRG Oncology
1-800-227-5463, ext. 4189

INDEX (09/23/16)

NRG ONCOLOGY

RTOG 0631

Phase II/III Study of Image-Guided Radiosurgery/SBRT for Localized Spine Metastasis

SCHEMA (09/23/16)

PHASE II COMPONENT	
R	
E	
G	**Radiosurgery/SBRT**:
I	Single fraction dose of 16 Gy
S	
T	
E	
R	

PHASE III COMPONENT			
S		**R**	
T	**Number of Spine Metastases**	**A**	**Arm 1**: **Radiosurgery/SBRT**:
R	1) 1 with a ≥5 NRPS score	**N**	Single fraction dose of 16 or 18 Gy**
A	2) 2-3 with ≥5 NRPS scores	**D**	
T		**O**	**Arm 2**: **External Beam Radiation Therapy**:
I	**Type of Tumor**	**M**	Single fraction dose of 8 Gy
F	1) Radioresistant tumor*	**I**	
Y	2) Other	**Z**	Randomization ratio (Arm 1: Arm 2) = 2:1
		E	
	Intended Radiosurgery/SBRT Single Fraction Dose**		
	1) 16 Gy		
	2) 18 Gy		

*Radioresistant tumors include soft tissue sarcomas, melanomas, and renal cell carcinomas.

**Patients randomized to Arm 1 (experimental arm) will be stratified according to the single fraction dose for image-guided radiosurgery/SBRT, using either 16 or 18 Gy as preferred by the treating physician.

See Section 5.0 for pre-registration requirements; see Section 6.0 for details of radiosurgery; see Section 11.2 and Appendix I for follow-up requirements.

Patient Population: (See Section 3.0 for Eligibility)
Patients with localized spine metastasis from the C1 to L5 levels (a solitary spine metastasis; 2 separate spine levels; or up to 3 separate sites); each of the separate sites must have a maximal involvement of 2 contiguous vertebral bodies.

Required Sample Size: **Phase II component: 43 patients**; **8/30/11**: **Completed**
(6/27/14) Phase III component: 352 patients

NRG Oncology Institution #
RTOG 0631 **ELIGIBILITY CHECKLIST (4/21/14)**
Case # **(page 1 of 3)**

_____ (Y) 1. According to a screening imaging study, is there localized spine metastasis from the C1 to L5 (a solitary spine metastasis); two separate spine levels; or up to 3 separate sites with a ≥5 NRPS score(e.g. C5, T5-6, and T12)?

_____ Specify screening imaging study (bone scan, PET, CT scan, or MRI)

_____ (Y) 2. Is the patient's Zubrod Performance Status 0-2?

_____ (Y) 3. Is the patient ≥ 18 years old?

_____ (Y) 4. Has a history and physical been performed within 2 weeks prior to registration?

_____ (Y) 5. Has a MRI of the involved spine been performed within 4 weeks prior to registration?

_____ (Y) 6. Has the Numerical Rating Pain Scale been performed within 1 week prior to registration with a score of ≥ 5 for at least one of the planned sites for spine radiosurgery?

_____ (Y) 7. Has the patient had a neurological exam within 1 week prior to registration to rule out rapid neurologic decline?

_____ (Y) 8. If epidural compression is present, is there a ≥ 3mm gap between spinal cord and the edge of the epidural lesion?

_____(Y) 9. If the patient has a paraspinal mass (≤ 5 cm in greatest dimension), is it contiguous with the spine metastasis?

___(Y/NA) 10. If a women of child bearing potential, has the patient had a negative serum pregnancy test within 2 weeks prior to registration?

_____(Y) 11. If a woman of child bearing potential or a sexually active male, is the patient willing to use effective contraception while on treatment?

_____(Y) 12. Has the patient signed the informed consent?

_____(N) 13. Does the patient have myeloma or lymphoma? other visceral metastasis and radioresistant tumors (including soft tissue sarcomas, melanomas, and renal cell carcinomas) are eligible).

_____(N) 14. Is the patient non-ambulatory?

_____(N) 15. Is there spinal instability due a compression fracture?

_____(N) 16. > 50% loss of vertebral body height?

_____(N) 17. Is frank spinal cord compression or displacement or epidural compression within 3 mm of the spinal cord?

_____(N) 18. Is bony retropulsion causing neurologic abnormality?

_____(N) 19. Has the patient received prior radiation to the index spine?

_____(N) 20. Is an MRI of the spine medically contraindicated for the patient?

(Continued on next page)

The following questions will be asked at Study Registration:
CREDENTIALING FOR IMRT and IMAGE-GUIDED SPINE RADIOSURGERY IS REQUIRED BEFORE REGISTRATION.

_____ 1. Institutional person randomizing this case?

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, iIs the patient eligible ?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials

_____ 6. Verifying Physician

_____ 7. Patient's ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Patient's Zip

_____ 14. Method of Payment

_____ 15. Any care at VA or military hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization Date

_____ 18. E-mail address of the RA following the patient

(Continued on next page)

_____(Y/N) 18. Blood kept for cancer research? Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 19. Urine kept for cancer research? Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Blood kept for medical research? Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease or heart disease)?

_____(Y/N) 21. Urine kept for medical research? Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Allow contact for future research? Have you obtained the patient's consent for allow someone from this institution to contact him or her in the future to ask him or her to take part in more research?

For Phase III Component Only:

_____(N/Y) 23. Did the patient agree to participate in the quality of life component?

_____ If no, provide the reason:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____ 24. Specify number of spine metastases
1. 1
2. 2-3

_____25. Specify type of tumor
1. Radioresistant (include soft tissue sarcomas, melanomas and renal cell carcinomas)
2. Other
Specify Other Tumor Type _____

_____26 Specify RT dose
1. 16Gy
2. 18Gy

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Spine Metastasis

Spine metastases are a common complication of cancer. While similar to other bone metastases in terms of vertebral bone involvement, spine metastases have unique clinical considerations. One is spinal bone pain, which is the most common initial presenting symptom. The other is that these metastases can present with a soft tissue mass at the paraspinal area or as an epidural compression. Therefore, patients with spinal metastases invariably have severe back pain, often with associated neurological problems, which can further compromise their performance status.

The main presenting symptom of spine metastases is back pain. Therefore, the primary goal of radiosurgery for spinal metastases is pain control (relief). The treatment of spine metastases has largely been with conventional fractionated radiotherapy. Although the most common regimen of radiotherapy has been 30 Gy in 10 fractions, the radiation dose-pain response has not been well settled. An early RTOG study for bone metastasis reported that low-dose short course radiotherapy was as effective as a high dose protracted regimen (Tong 1982). Recently, RTOG 97-14, which randomized the treatment of bone metastasis between a single dose of 8 Gy and 10 fractions of 3 Gy for a total dose of 30 Gy, also showed a similar result. However, the duration and rate of pain control of bone metastases was limited by the conventional method of radiotherapy in both arms (Hartsell 2005). In a subgroup of patients with spine metastases in this study, only 61% of patients experienced partial or complete pain relief at 1 month post-treatment. Recently, there has been an increasing trend of diagnosing more localized spine metastases (i.e., oligometastases), although the true incidence of solitary spine metastasis is not known. These patients may have a prolonged survival time. Therefore, there is pressing need to improve the pain control of patients with spine metastases, which may be connected to an improvement in quality of life.

Despite the common occurrence of spine metastases, there have been few prospective studies for this large group of patients (Greenberg 1980; Young 1980; Maranzano 1995; Helweg-Larsen 1996; Patchell 2005). It is evident, from these studies, that a single dose of 8-10 Gy is equivalent to a fractionated regimen of 30 Gy in 10 fractions. This suggests that a further increase in the single dose of radiation may improve the rate of pain control. The difficulty is that there is a dose-limiting organ, the spinal cord, within close proximity to the vertebral body, and spine metastases often are present with epidural tumor masses. Therefore, accurate targeting and radiation intensity-modulation will be required to minimize the spinal cord dose. In this effort, radiosurgery has emerged as an innovative treatment option for spinal metastases. While the spine region does have the benefit of minimal breathing-related organ movement and easy imaging, safely delivering a more intensive dose of radiation requires not only precise targeting due to the proximity of the spinal cord, but also accurate treatment planning and delivery.

1.2 Radiosurgery/SBRT of Localized Spine Metastasis

Preclinical physical and dosimetric studies have demonstrated the applicability of patient positioning, immobilization, and dosimetric characteristics of spinal radiosurgery for spine metastases (Yin 2002; Yin 2002b). The first approach to establish clinical feasibility was to determine the accuracy and precision of radiosurgery to treat the spine and epidural/paraspinal tumors that are adjacent to the spinal cord. This clinical study demonstrated targeting accuracy within 1.5 mm for actual patient treatment (Ryu 2003). The accuracy of radiosurgical targeting for spine has been reported with various technologies (Ho 2007; Yin 2008).

Subsequent clinical experience with single dose radiosurgery for spinal metastasis showed the efficacy of radiosurgery for pain control and improvement of neurological function in patients with epidural compression. In these studies, there was rapid pain relief reported with a median time to pain relief of only 2 weeks, with pain control seen in some patients as early as within 24 hours (Ryu 2003; Gertzen 2005; Degen 2005; Ryu 2004). Median duration of pain control in the treated spine region was 13.3 months (Ryu 2008). Other investigators also demonstrated similar results of pain control in patients with spine metastasis (Gertzen 2005; Degen 2005; Gertzen 2006; Gertzen 2005b). Quality of life also was improved secondary to pain control (Degen 2005). Local tumor control at the treated spine was achieved in 95% of the patients. Recurrence at the immediately adjacent vertebrae was less than 5% (Ryu 2004). Patients with oligometastasis had a longer survival with more effective local treatment of the spine metastasis (Ryu 2007). This

suggests that a more intensive treatment may be appropriate for patients with localized spine metastases in order to improve their clinical outcome and quality of life. A single institution clinical trial of radiosurgery for epidural spinal cord compression showed that thecal sac patency was achieved in 82% of patients by radiographic reduction of epidural or paraspinal tumors (Ryu 2008c).

Spinal cord as the dose-limiting critical organ at risk is a key concern. Because of the nature of radiosurgery with rapid dose fall-off, there is a radiation dose gradient within the diameter of the spinal cord. The result of accumulated dose volume histogram (DVH) analyses of the spinal cord in 230 procedures at Henry Ford Hospital showed a partial volume tolerance of the spinal cord of 10 Gy to the 10% cross-sectional area of the cord, provided that the spinal cord is defined as 6 mm above and below the radiosurgery target volume (Ryu 2007). Other investigators used slightly different criteria of defining the spinal cord dose: these were a maximum dose of 12-14 Gy at the surface of an MRI-defined or myelogram-defined spinal cord (Chang 2007) or a maximum dose of 10 Gy in a myelogram-defined spinal cord (Yamada 2008). Taken together, these dose criteria were in a similar range. Therefore, we chose to use the spinal dose constraint as 10 Gy to 10 % of the spinal cord defined as a maximum of 6 mm above and below the radiosurgery target.

1.3 Selection of Radiosurgery Dose **(8/30/11)**

A radiation dose-response relationship for pain control has not been established. However, there is a trend for a radiation dose-pain control relationship when all the studies are compiled. A recent meta-analysis of ten randomized trials containing single fraction radiotherapy for painful bone metastasis showed single-fraction radiation (median 8 Gy, range 8-10 Gy) achieved a complete pain response of 33.4%, and an overall response rate of 62.1% (Wu 2003). Large scale clinical trials using single fraction radiation doses of 8 Gy resulted in similar pain control of bone metastasis (Hartsell 2005; Bone Pain Trial Working Party 1999; Steenland 1999). Therefore, the phase III portion of this trial will use either 8 Gy as the prescribing radiation dose; 3-dimensional conformal beam arrangement is also allowed per the treating physician's discretion.

Radiosurgery experiences recently have been reported with a single fraction of higher radiation doses for spinal metastasis. The majority of the spine metastases consistently responded to the higher doses of radiosurgery. Although the results cannot be directly compared to each other, these results suggest a trend towards a higher overall pain control with higher radiation doses (Ryu 2003; Ryu 2004; Gertzen 2006; Gertzen 2005b). There is no threshold dose that can be firmly stated. Based on the Henry Ford Hospital experience of radiosurgery dose escalation from 10 Gy to 20 Gy in 2 Gy increments, there was a strong trend for increasing pain relief with higher radiation doses, particularly when a dose ≥ 16 Gy was employed (Ryu 2008; Ryu 2007).While there was no statistically significant difference, the sample size may have been the main limiting issue to detect a statistical difference in the dose-response analysis. When the radiosurgery dose was ≥ 16 Gy, the probability of pain relief was reached in over 80% of the patients. The experience of the University of Pittsburgh also showed consistent results of pain relief with a median dose ≥ 16 Gy (Gerzten 2005; Gertzen 2005b; Gertzen 2006). Therefore, the phase III component of this study will use 16 or 18 Gy in 1 fraction. The spinal cord constraint is 10 Gy to the 10% partial spinal cord volume (spinal cord defined as a maximum of 6 mm above and below the target volume) [Ryu 2007].

Additional experience of radiosurgery with higher doses for spine metastasis suggest that a higher (than 16 Gy) radiosurgery dose was required to achieve similar pain relief, particularly in radioresistant tumors including soft tissue sarcoma, melanoma, and renal cell carcinoma as well as other tumors. (Gerszten 2005c; Nguyen 2010, Yamada 2008). Therefore, the phase III component of this study will use a radiosurgical dose of 16 Gy or 18 Gy per treating physician's discretion and institutional experience. Maximum tolerated dose (MTD) has not been defined in spine radiosurgery, as the MTD of the spinal cord is not known. In this clinical trial, the proposed prescription doses are readily achievable with the defined spinal cord tolerance constraint described in Sections 1.2 and 6.3.1.2.

1.4 Advantages of Image-Guided Radiosurgery **(8/30/11)**

The potential advantages of using image-guided radiosurgery for spine metastasis are many. First, pain control is rapid and durable. Second, since only the involved spine will be treated, bone

marrow will be preserved. The spine is a key blood-forming organ. By reducing the radiation target, organ preservation of the bone marrow can be achieved. This will help facilitate continuation of systemic therapy, which is often essential for this group of patients. Third, radiosurgery is only one treatment as opposed to 10-15 visits for conventional fractionated radiotherapy. It is more convenient for the patient. Equally important is that a single session of radiosurgery does not interfere with ongoing chemotherapy schedules. Fourth, radiosurgery has the potential to be used for decompression of epidural compression. Last, radiosurgery is a non-invasive treatment; it has the potential to reduce the necessity of invasive open surgery in these patients. The non-invasiveness and shortened treatment time provided by spine radiosurgery has great potential to improve the quality of life in this group of patients who can have debilitating conditions and/or neurological deficits. Thus, it is anticipated that in the future image-guided radiosurgery may become a standard of care to treat localized spine metastasis with or without spinal cord compression. Indeed, as this technology is becoming so widely available, this clinical trial is critical to avoid both under-utilization and over-utilization of this emerging technique.

It is important to first study this emerging technique of spine radiosurgery in a phase II trial within a national cooperative group. This phase II study will assess the experience of spine radiosurgery in the NRG Oncology community, which is the optimum forum to test and develop a new radiotherapeutic technology. Once the single arm phase II component is completed and the efficacy of spine radiosurgery is demonstrated, the phase III component will proceed to determine whether spine radiosurgery improves the treatment outcome of spine metastasis as compared to conventional radiotherapy. The phase III component will randomize patients to directly compare a single dose of external beam radiation (8 Gy) versus SBRT given in one fraction (16 Gy or 18 Gy). The result will indeed demonstrate whether or not there is radiation dose-response in pain control of bone metastasis.

1.5 Hypothesis **(8/30/11)**

In the prior RTOG study for bone metastases, 97-14, the duration and rate of pain control of bone metastases was limited by conventional radiotherapy (single dose of 8 Gy or 10 fractions of 3 Gy for a total dose of 30 Gy) [Hartsell 2005]. Although previous results defined partial pain relief as an improvement of ≥ 2 points, the current trial will define partial pain relief as an improvement of ≥ 3 points to ensure stringent pain control. Complete pain relief will remain defined as no pain, as indicated by a post-treatment score of 0. Both partial and complete pain relief require no increase in narcotic medication. In RTOG 97-14, 253 patients (29% of total) were treated to the spine. The pain response rate was 51% at 3 months in these patients.

The goal of the phase II component of this study is to demonstrate the technical feasibility of treating spine metastases with image-guided radiosurgery/SBRT in the NRG Oncology setting. Treatment compliance will be evaluated according to the radiosurgery guidelines (see Section 6.0). Based on the RTOG experience of treating lung cancer with SBRT, the target rate for successful treatment delivery is 85% of patients successfully treated with SBRT for spine metastasis.

The hypothesis of the phase III component, in which patients will be randomized to image-guided radiosurgery/SBRT in a single fraction dose of 16 or 18 Gy (experimental arm) OR conventional external beam radiotherapy in a single dose of 8 Gy (control arm based on the RTOG 97-14 results) is that image-guided radiosurgery/SBRT will result in a 40% improvement (from 51% to 70%) in the proportion of patients experiencing pain relief at 3 months as compared to the external beam radiotherapy. Patients randomized to Arm 1 (experimental arm) will be stratified according to the single fraction dose for image-guided radiosurgery/SBRT, using either 16 or 18 Gy as preferred by the treating physician.

1.6 Primary Endpoint: Numerical Rating Pain Scale (NRPS) **(8/30/11)**

1.6.1 The primary endpoint is pain control at the treated site(s) at 3 months post-treatment. Pain recurring or progressing prior to 3 months post-treatment is considered a failure. For evaluation of pain relief, the Numerical Rating Pain Scale (Jensen 1999) will be used. The NRPS is a simple measure of pain on an 11-point scale (0-10). In the study comparing the reliability and validity of several measures of pain intensity, the composites of 0-10 ratings have been shown to be useful when maximal reliability was necessary in studies with relatively small sample

sizes or in clinical settings in which monitoring of changes in pain intensity in individuals is needed.

1.6.2 *Scoring Pain*

1.6.2.1 Solitary Spine Lesion

The NRPS will document the status of pain at the treated single spine site.

1.6.2.2 Multiple Spine Lesions

When multiple spine lesions are treated, the index spine lesion will be used to assess the pain response. The index spine lesion is defined as the spine lesion with the highest pretreatment pain score. If a patient has > 1 lesion with the same maximal pain score, the index lesion will be the most cephalad of these lesions. For example, for a patient who has 3 spine lesions to be treated: 1) C5 lesion with pain score of 4; 2) T2-3 lesion with pain score of 6; and 3) T12 lesion with pain score of 6. The index lesion in this case would be T2-3 lesion, as **it is the most cephalad lesion among the lesions with the highest pain score. If, however, the same patient had a pretreatment score at T12 of 7 (and the rest of the scores remained the same), the T12 lesion would be the index lesion.**

1.6.2.3 Type of Tumor

The stratification between radioresistant tumors and other tumors is due to the similarity of their expected responses. Radioresistant tumors include soft tissue sarcoma, melanoma, and renal cell carcinoma. It has been shown that these types of tumors, specifically melanoma and renal cell carcinoma, appear to have similar responses compared to any other tumor (Gerszten 2005 (c); Nguyen 2010). Thus, these types of tumors are eligible for the study treatment but will be stratified among the treatment groups to not bias the results.

1.6.3 *Definition of Pain Response*

1.6.3.1 Complete pain relief is defined as a pain score of 0 at the index site at 3 months post-treatment. Complete pain relief is based on no increase in narcotic pain medication.

1.6.3.2 Partial pain relief is defined as a reduction in the numerical pain score of ≥ 3 (i.e., an improvement of at least 3 points from the baseline NRPS) at the index site, as long as none of the other treated lesions have increased in pain score and as long as the patient did not require an increase in the level of narcotic pain medication. Patients who require an increase in narcotic pain medication will not be scored as having partial pain relief, even if their pain score has improved by at least 3 points on the scoring system. (Note: If a patient can only give one pain score for all sites, this score will be used for all treated sites at that time point, and the most cephalad lesion will be defined as the index lesion).

1.6.3.3 Stable response is defined as a post-treatment pain score the same as or within 2 points of the baseline pain score at the index site with no increase in narcotic pain medication.

1.6.3.4 Progressive response is defined as a post-treatment increase of at least 3 points from the baseline pain score at the index site.

1.6.4 *Evaluation of Pain Response*

Complete or partial pain relief or a stable response at the index site requires no increase in narcotic pain medication and excludes progressive response at the secondary treated site(s). Although complete pain relief is the best outcome, partial relief also is a satisfactory outcome. Therefore, patients with complete or partial pain relief will be considered responders. Patients with complete or partial pain relief at the index site but a progressive response at the secondary site(s) will be considered non-responders.

1.7 Quality of Life Measurements (09/23/16)

It is hypothesized that quality of life (QOL) will improve after radiosurgery due to rapid and durable pain control after spine radiosurgery. Indeed, in one study, QOL improved secondary to pain control (Degen 2005). In the current study, we will measure the QOL after radiosurgery using the Functional Assessment of Cancer Therapy: (FACT-G), the Brief Pain Inventory (BPI), and the EuroQol (EQ-5D).

1.7.1 *Brief Pain Inventory (BPI)*

The pain originating from the spine directly affects the patient's QOL because the spine is the major weight-bearing area. The Brief Pain Inventory (BPI), developed by Daut, et al. (1983) is a 17-item patient self-rating scale assessing demographic data, use of medications, as well as the sensory and reactive components of pain. The BPI includes items that will address components of sensory pain, including severity, location, chronicity, and degree of relief due to therapy. The BPI also has items that address reactive pain components, such as depression, suffering, and the perceived availability of relief. The scale is from 0-10, and there are

breakpoints between scores of 4 and 5 and between 6 and 7, indicating that mild pain correlates with scores of 1-4, moderate pain with 5-6, and severe pain with scores of 7-10. Respectable reliability has been demonstrated using test-retest item correlation (e.g., for worst pain, r = .93). Issues of the validity and reliability of the BPI have been examined in detail (Jensen 1999; Daut 1983). The BPI's ease of translation and brief administration have made it a frequently used tool in clinical trials where reduction or prevention of pain are the outcome measures. The BPI was previously used successfully in RTOG 97-14 studying patients with bone metastases treated with radiation therapy.

The BPI asks patients to rate their pain for the last week on 0-10 scales at its 'worst', 'least', 'average', and 'now.' The scales are presented on a 10 cm line, with each number equidistant from the next. Each scale is bounded by the words 'no pain' at the 0 end and 'pain as bad as you can imagine' at the other. Using the same type of scales, patients also are asked to rate how their pain interferes with several quality of life domains including activity, walking, mood, sleep, work, and relations with others. These scales are bounded by 'does not interfere' at the 0 end and 'interferes completely' at the other. Patients also are asked to estimate the pain relief they are receiving from their pain treatment (in percent), to locate areas of pain on a human figure, and to estimate the cause of their pain (cancer disease, cancer treatment, or non-cancer). The patient can complete the BPI in approximately 5 minutes, and the assessment is available in 12 languages.

Issues of the validity and reliability of the BPI have been examined in detail (Daut 1983; Cleeland 1989). The BPI is considered as the FDA standard for a pain assessment tool. The typical standard deviation for the item "worst pain" in most cancer populations is 2.4. Therefore, the finding of a one-point difference in the "worst pain" item at different times or between two comparative groups is considered significant. Translations can be accessed at http://www.mdanderson.org/departments/prg/; click on "symptom assessment tools".

1.7.2 *The Functional Assessment of Cancer Therapy (FACT-G)*

Assessment of pain and its relief also are affected by multiple factors, including the patient's understanding regarding the nature of pain, and emotional and social background. Therefore, as in RTOG 97-14, the Functional Assessment of Cancer Therapy (FACT-G), v. 4.0, also will be collected. The FACT-G is a commonly used tool measuring the multidimensional components of health related quality of life (HRQOL) across 4 scales: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items) and functional well-being (7 items) The FACT, developed by Cella, et al. (1993)., is a five point patient self rating scale (from "not at all" to "very much"). Test-retest reliability is high for the subscales with correlation coefficients ranging from a high of .88 for physical well-being to .82 for social and emotional well-being. It is written at the 4th grade reading level, and patients can complete the FACT-G in 5-10 minutes. The FACT has been translated into more than 25 languages, and translations are accessible at the FACIT web site, http://www.facit.org/FACITOrg/Questionnaires.

1.7.3 *The EuroQol (EQ-5D)*

The EuroQol (EQ-5D) instrument is intended to complement other forms of QOL measures, and it has been developed to generate a generic cardinal index of health, thus giving it considerable potential for future use in economic evaluation. The EQ-5D is a two-part, patient-completed questionnaire that takes approximately 5 minutes to complete(Rabin 2001; Schulz 2002). The first part consists of 5 items covering 5 dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1=no problems; 2= moderate problems; and 3=extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added (Badia 1998). The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at http://www.euroqol.org/. The inclusion of the EQ-5D is exploratory, as it allows one to analyze important issues related to quality adjusted survival and cost utility analyses and determine if the instrument should be included in a future phase III trial.

2.0 OBJECTIVES

2.1 Primary Objective (8/30/11)

2.1.1 Phase II Component

Determine the feasibility of successfully delivering image-guided radiosurgery/SBRT for spine metastases in a cooperative group setting

2.1.2 Phase III Component

Determine whether image-guided radiosurgery/SBRT (single dose of 16 or 18 Gy) improves pain control (as measured by the 11 point NRPS) as compared to conventional external beam radiotherapy (single dose of 8 Gy)

The endpoint is complete or partial pain relief at the treated index site at 3 months, (as measured by the 11 point NRPS). Complete pain relief is defined as a score of 0 on the NRPS, with no increase in narcotic pain medication. Partial pain relief is defined as an improvement from the baseline NRPS of at least 3 points on the rating scale (and no progressive pain response at any other treated lesion[s], with no increase in narcotic pain medication).

2.2 Secondary Objectives (Phase III Component) (09/23/16)

2.2.1 Determine whether image-guided radiosurgery/SBRT improves the rapidity of pain response at the treated site(s) as compared to conventional external beam radiotherapy, as measured by the NRPS;

2.2.2. Determine whether image-guided radiosurgery/SBRT increases the duration of pain response at the treated site(s), as compared to conventional external beam radiotherapy, as measured by the NRPS;

2.2.3 Compare adverse events between the two treatments according to the criteria in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0;

2.2.4 Evaluate the long-term effects (24 months) of image-guided radiosurgery/SBRT on the vertebral bone (such as compression fracture) and the spinal cord by MRI;

2.2.5 Evaluate the potential benefit of image-guided radiosurgery/SBRT on change in and overall quality of life, as measured by the Functional Assessment of Cancer Therapy-General (FACT-G); in pain as measured by the Brief Pain Inventory (BPI); and in health utilities as measured by the EuroQol (EQ-5D);

2.2.6 To implement a well-controlled specimen handling/storage process to facilitate future laboratory correlative studies.

3.0 PATIENT SELECTION (11/22/13)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

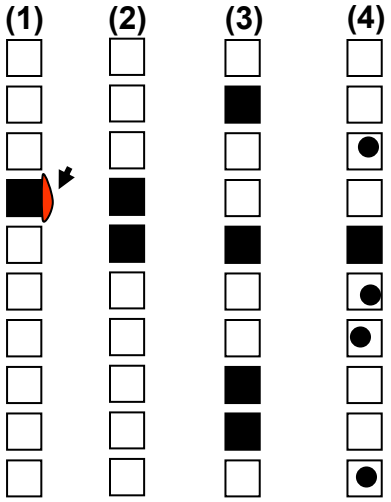
For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (09/23/16)

3.1.1 The patient must have localized spine metastasis from the C1 to L5 levels by a screening imaging study [bone scan, PET, CT, or MRI] (a solitary spine metastasis; two separate spine levels; or up to 3 separate sites [e.g., C5, T5-6, and T12] are permitted.) Each of the separate sites may have a maximal involvement of 2 contiguous vertebral bodies. Patients can have other visceral metastasis, and radioresistant tumors (including soft tissue sarcomas, melanomas, and renal cell carcinomas) are eligible.

See Figure 1 below for a depiction of eligible metastatic lesions: 1) a solitary spine metastasis; 2) two contiguous spine levels involved; or 3) a maximum of 3 separate sites. Each of the separate sites may have a maximal involvement of 2 contiguous vertebral bodies. Epidural compression (arrow) is eligible when there is a ≥ 3 mm gap between the spinal cord and the edge of the epidural lesion (see Section 3.1.10). A paraspinal mass ≤ 5 cm is allowed (see Section 3.1.11).

Figure 1: Diagram of Eligible Metastatic Lesions



3.1.1.1 There can be multiple small metastatic lesions shown in other vertebral bodies as shown in diagram (4) above. The metastatic lesion of each spine should be less than 20% of the vertebral body as opposed to the diffuse vertebral involvement. These small lesions are often seen in the MRI even when bone scan or PET was negative. Most of these lesions are not clinically required to be treated and are therefore not included in the target volume of this protocol. Only the painful spine (pain score≥ 5) is to be treated .

3.1.2 Zubrod Performance Status 0-2;

3.1.3 Age ≥ 18;

3.1.4 History/physical examination within 2 weeks prior to registration;

3.1.5 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;

3.1.6 Women of childbearing potential and male participants who are sexually active must agree to use a medically effective means of birth control;

3.1.7 MRI (contrast is not required but strongly recommended) of the involved spine within 4 weeks prior to registration to determine the extent of the spine involvement; an MRI is required as it is superior to a CT scan in delineating the spinal cord as well as identifying an epidural or paraspinal soft tissue component. Note: If an MRI was done as a screening imaging study for eligibility (see Section 3.1.1), the MRI can be used as the required MRI for treatment planning.

3.1.8 Numerical Rating Pain Scale within 1 week prior to registration; the patient must have a score on the Scale of ≥ 5 for at least one of the planned sites for spine radiosurgery. Documentation of the patient's initial pain score is required. Patients taking medication for pain at the time of registration are eligible.

3.1.9 Neurological examination within 1 week prior to registration to rule out rapid neurologic decline; **see Appendix III for the standardized neurological examination.** Patients with mild to moderate neurological signs are eligible. These neurological signs include radiculopathy, dermatomal sensory change, and muscle strength of involved extremity 4/5 (lower extremity for ambulation or upper extremity for raising arms and/or arm function).

3.1.10 Patients with epidural compression are eligible provided that there is a ≥ 3 mm gap between the spinal cord and the edge of the epidural lesion.

3.1.11 Patients with a paraspinal mass ≤ 5 cm in the greatest dimension and that is contiguous with spine metastasis are eligible.

3.1.12 Patients must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (5/6/13)

3.2.1 Histologies of myeloma or lymphoma;

3.2.2 Non-ambulatory patients;

3.2.3 Spine instability due to a compression fracture;

3.2.4 > 50% loss of vertebral body height;

3.2.5 Frank spinal cord compression or displacement or epidural compression within 3 mm of the spinal cord;
3.2.6 Patients with rapid neurologic decline;
3.2.7 Bony retropulsion causing neurologic abnormality;
3.2.8 Prior radiation to the index spine;
3.2.9 Patients for whom an MRI of the spine is medically contraindicated;
3.2.10 Patients allergic to contrast dye used in MRIs or CT scans or who cannot be premedicated for the use of contrast dye.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (Phase III Component Only) (8/30/11)

4.1.1 The patient will complete the baseline Numerical Rating Pain Scale (NRPS) on the day of treatment identifying how much pain they are having at the index spine lesion to be treated. The patient can be on pain medication.

Note: The Numerical Rating Pain Scale (NRPS) used to determine eligibility (a required score of ≥ 5; see Section 3.1.8) will not be used to assess treatment response. Documentation of the patient's initial pain score is required. Treatment response will be assessed by the baseline NRPS completed on the day of treatment. Patients whose day of treatment NRPS score is < 5 remain eligible for the study, will receive treatment, and will be followed per protocol specifications.

4.1.2 If the patient consents to participate in the quality of life component of the study, sites are required to administer the following baseline quality of life questionnaires prior to the start of protocol treatment: The Functional Assessment of Cancer Therapy-General (FACT-G); the Brief Pain Inventory (BPI), and the EuroQol (EQ-5D).

5.0 REGISTRATION PROCEDURES (09/23/16)

Access requirements for OPEN, Medidata Rave, and TRIAD: Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account.
The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures below for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

5.1 Investigator Registration Requirements (09/23/16)

Prior to the recruitment of a patient for this study, investigators must be registered members of a Lead Protocol Organization. Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually. Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature;
- a current ***Curriculum Vitae*** (CV);
- a completed and signed ***Supplemental Investigator Data Form*** (IDF);
- a completed ***Financial Disclosure Form*** (FDF) with an original signature.

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the *CTEP Investigator Registration Help Desk* by email at <pmbregpend@ctep.nci.nih.gov>.

5.2 Pre-Registration Requirements for Spine Radiosurgery/SBRT (09/23/16)

5.2.1 The institution must complete or update all relevant parts of the NRG Oncology Facility Questionnaire: All questions in Part I (General Information for 3D-CRT and IMRT), in Part II (Information Specific to IGRT), and in Part III (Information for Heterogeneity Corrections and Motion Management) must be completed [available on the IROC Houston (formerly the Radiology Physics Center/RPC) web site at http://irochouston.mdanderson.org/] and send it to NRG Oncology for review prior to entering any cases, A TRIAD account for digital data submission must also be set-up. NRG Oncology will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study..

5.2.2 In addition to the steps described in Section 5.1.1, credentialing for spine radiosurgery includes the process of **irradiating the spine phantom provided by IROC Houston.** Instructions for requesting and irradiating the spine phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed this requirement.

5.3 Additional Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT) (09/23/16)

5.3.1 IGRT Credentialing Process

5.3.1.1 Prior to entering patients on this study, institutions must perform a verification study. In order to complete the verification study, the institution must do the following:

- Submit a series of planning and localization images along with a spreadsheet of IGRT data via TRIAD from an anonymized patient treated similarly to 0631 but **not** accrued to the study. Post-treatment imaging is mandatory for credentialing.
- The Medical Physics Co-Chair, Dr. Yin, will review the images and spreadsheet and upon his approval of this data, NRG Oncology will notify the institution that this part of the credentialing is complete and the institution can continue to enroll patients on 0631.

See the NRG Oncology/RTOG web site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0631 to obtain the spreadsheet. Since this study involves a single fraction treatment of the spine, simulation images and the treatment plan, onboard localization images (including setup images of simulation position prior to correction, images after reposition prior to treatment, and images of post-treatment) are required. Acquisition of additional images acquired during treatment are encouraged but not required. Pretreatment, during treatment, and post-treatment images may include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage [MV] or kilovoltage [KV] x-rays). Additionally, orthogonal (MV or KV) 2D electronic images can be used. IGRT data and the completed spreadsheet are submitted to TRIAD. Select Benchmark submission.

5.3.1.2 *Tolerance Levels for IGRT*

Three-dimensional views of gross tumor and other adjacent normal tissue structures, especially the spinal cord, are recommended as reference at the discretion of the treating radiation oncologist. Shifts of patient treatment position can be made based on the pretreatment images. After the position adjustments, the final accuracy of positioning should be < 2 mm identified from the post-shift images, compared with the pre-treatment position.

For those institutions that plan to use orthogonal images for target localization and position adjustment, placement of fiducial markers such as seeds (typically 3 or more) in or outside the gross tumor is recommended. Fiducial markers are often placed under the guidance of

ultrasound or CT scan. An orthogonal view of fiducial markers and/or bony anatomy adjacent to the target volume can be used as a standard method. After shifts are made based on the pretreatment images and after the position adjustments, the final accuracy of positioning should be < 2 mm identified from the post-shift images, compared with the pre-treatment position.

5.4 Digital RT Data Submission to NRG Oncology Using TRIAD (09/23/16)

TRIAD is the American College of Radiology's (ACR) image exchange application..
TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG Oncology users should contact your site Lead RA to be added to your site roster. You must have your CTEP IAM username on your Roster update request. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG website Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.5 Regulatory Pre-Registration Requirements (09/23/16)

5.5.1 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Requirements for RTOG 0631 Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval letter
- IRB/REB Approved Informed Consent (English and native language versions*)
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to NRG Headquarters (described below).
- IRB/REB registration number renewal information as appropriate.
- CTSU RT Facilities Inventory Form

- NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Imaging and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal
EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX: 215-569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Checking Your Site's Registration Status:
You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.5.2 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

5.5.2.1 **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from NRG Oncology prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx

5.5.2.2 **For institutions that have an approved LOI for this protocol:**
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.6 Registration (09/23/16)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

5.6.1 Oncology Patient Enrollment Network (OPEN)
Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. . To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records. If it is necessary to reprint the randomization confirmation or the transmittal form, they can be reprinted through Coordinator Online via the **View a Patient Entry Report** under Patient Entry.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG Oncology for assistance with web registration at websupport@acr.org or 215-574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (8/30/11)

The Principal Investigator, Samuel Ryu, MD, and Co-Chairs will perform a rapid review of the treatment plan for the first 2 radiosurgery/SBRT cases from each institution **prior to the institution delivering any protocol treatment on the phase II component or Arm 1 of the phase III component**. Institutions should allow 3 business days for each case to be received, processed, and reviewed. If the plan must be resubmitted, it will be given a rapid review (within 3 business days). Treatment plans for subsequent patients enrolled at a site will not be reviewed prior to delivery of treatment, but a review will be performed at a later date to evaluate protocol compliance.

Questions regarding spine radiosurgery/SBRT should be directed to Dr. Ryu (preferably by e-mail, sryu1@hfhs.org, or alternatively by phone, 313-916-1027).

Patients may receive external beam irradiation to other sites, brachytherapy (HDR or LDR), or a combination of external beam irradiation and brachytherapy at the discretion of the treating physician. Dose/duration also will be at the discretion of the treating physician. However, the spine radiosurgery/SBRT and other radiotherapy must not occur at the same time or overlap.

Patient registration must be done within 4 weeks after MRI of the involved spine. Note: The patient will complete the baseline Numerical Rating Pain Scale on the day of treatment.

NOTE: Sections 6.1-6.7 (below) provide information regarding treatment with radiosurgery/SBRT for the phase II and phase III (Arm 1) components of this study. See Section 6.6.2 for IGRT requirements for Arm 1 patients. If the patient is randomized to Arm 2 of the phase III component, see Section 6.8 for details of external beam radiotherapy.

6.1 RADIOSURGERY/SBRT, PHASE II AND PHASE III (ARM 1) COMPONENTS (8/30/11)

IMRT OR OTHER DOSE PAINTING TECHNIQUES ARE REQUIRED FOR RADIOSURGERY/SBRT. 3D-CRT IS NOT PERMITTED.

6.1.1 Dose Specifications

6.1.1.1 *Dose Fractionation*

Patients treated with radiosurgery/SBRT will receive a prescribed dose of 16 or 18 Gy in 1 fraction to cover at least 90% of the defined target volume (see Section 6.3.1.1). The radiation dose will be chosen based on the treating physician's discretion and achievement of spinal cord dose constraints as described below. Coverage of target volume < 90% but > 80% is a minor violation, and any coverage < 80% is a major deviation (see Section 6.3.2).

See cord dose/volume constraints in Section 6.3.1.2.

When the patient has multiple spine levels treated, the spinal cord constraint is applied to **each treated spine level. The spinal cord volumes are defined based on the image fusion of simulation CT and MRI with T2-weighted and T1-weighted images with contrast. In addition to the spinal cord DVH constraints, the treating physician should**

review each cross-sectional image to check if there is any excessive radiation dose distribution to the spinal cord.

Radiosurgery should not be used for any cases with a spinal cord dose exceeding the constraints described in this study. Any spinal cord dose that does not meet these criteria is a major deviation (see Section 6.4.1.1).

6.1.1.2 *Physical Factors*

Photon (x-ray) beams produced by linear accelerators with energies 4-18 MV will be allowed, preferably using photon beams with energy of 6 MV or less. IMRT or other dose painting techniques are allowed. Proton beams, and other charged particle beams (including electrons, heavy ions) are not allowed. Gamma Knife® or Perfexion™ treatment is not allowed.

6.1.1.3 *Premedications*

No premedications are necessary.

Pain control to help position the patient for the purpose of treatment (not for long-term pain control) is permitted to decrease patient movement due to pain. Note: Narcotics can be used or increased for the purposes of patient positioning for radiosurgery, as clinically necessary; however, the patient should return to the prior level of pain medication after radiosurgery.

If it is necessary to minimize patient's anxiety about the treatment and disease condition or for immobilization purposes, medications such as alprazolam or lorazepam are allowed.

No steroid premedication is indicated, and it is recommended that all patients receiving corticosteroids begin tapering them immediately after radiosurgery.

6.2 Immobilization, Simulation, and Localization (11/22/13)

6.2.1 *Patient Positioning*

Patients must be positioned in a stable supine position capable for reproducibility of positioning and immobilization from simulation to treatment, allowing the patient to feel as comfortable as possible. Positions uncomfortable for the patient should be avoided to prevent unnecessary movement. A prone position is not allowed. A variety of immobilization systems may be utilized including vacuum bag, alpha cradle, or stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the treatment delivery coordinate system. In addition, for cervical spine or cervicothoracic junctional areas, a rigid head and neck immobilization device should be used. Patient immobilization must be reliable enough to achieve the accuracy requirement of image-guidance (see Section 5.2.1.2).

6.2.1.1 Repositioning for Treatment

It is important to reproduce the treatment position. Pain can cause unintended movement, which can prolong treatment time and require repositioning. Therefore, it is important to allow the patient to feel as comfortable as the patient felt during the simulation.

Spine radiosurgery/SBRT is an image-guided procedure. Body frames based only on frame fiducials are not be considered adequate image guidance. Recent development of in-room (or onboard) imaging technology has improved the stereotactic target localization and visualization under image-guidance. These methods can be used where available. Coordinate systems between imaging system and delivery system should be aligned for spine radiosurgery/SBRT. Image data from the repetition of the image-guided maneuver near (prior to the last delivered beam) or at the end of the treatment should be sent to the ITC (see Section 6.2.3).

The treating physician can decide the day of treatment. Treatment can be given on the same day as positioning and simulation when feasible; however, it is not required. It is strongly recommended that institutions treat the patient no later than the day following simulation. For the purpose of rapid review of the first case, institutions should allow 3 business days for their initial case to be received, processed, and reviewed (as specified in Section 6.0).

6.2.2 *Simulation*

CT simulation will be performed with proper patient positioning and immobilization. It is important to ensure that the target volume is within the attainable range of the frame-based or frameless stereotactic device. CT will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. The use of intravenous contrast is strongly recommended as this will help delineate the tumor and normal tissues. Contrast will help visualize the soft tissue and adjacent normal tissues. Axial acquisitions with gantry 0 degrees will be required with slice thickness of ≤ 2.5-3 mm, depending on the manufacturer's selected slice thicknesses. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

6.2.3 *Localization*

Acceptable image-guided techniques include the following. The accuracy of localization should be less than 2 mm from simulation/planning to the end of treatment.

1. Cone-beam CT equipment attached to the linear accelerator, using either the treatment beam or an auxiliary kV x-ray head to obtain multiple projection images for volume reconstruction;
2. Spiral dose delivery equipment that uses the treatment beam to gather helical CT information for image guidance;
3. Any equipment that can produce stereoscopic planar views of the patient in the treatment position, capable of localizing anatomic points in space or viewing implanted fiducial markers. It can use the treatment beam with a standard electronic portal imaging device (EPID) or a kV x-ray source with opposed imaging panel.
4. A standard diagnostic-quality CT scanners positioned in the treatment room and geometrically coupled (e.g., on rails) with the treatment equipment.

Although film procedures could fall under the description given in item 3 above, there are certain limitations that make it difficult to extend the definition to include this technology. A major limitation for film is that it must be scanned with a densitometer to convert this information to digital data. Additionally, in order to use this digital data in the fusion process, the film must be held perpendicular to the direction of the beam. Although possible, this geometry is not available on most linear accelerators. Thus, radiographic film is not allowed as an image-guided technique for this study. However, film is allowed as a double check to verify the positioning obtained with any of the accepted IGRT techniques.

Institutions are required to save and forward all the images used for patient setup adjustments. These images must be sent in DICOM or JPEG format to TRIAD. This must include both the IGRT images and the treatment planning images.

6.3 Treatment Planning/Target Volumes (8/30/11)

6.3.1 *Target Definition*

Image fusion between MRI (gadolinium contrast T1-weighted and T2-weighted images) and simulation CT is required for delineation of both the soft tissue tumor component and the spinal cord. Special attention should be taken with image fusion when simulation CT and MRI images are taken in different imaging positions. Spine curvature of MRI and CT simulation usually is not aligned well. In this situation special attention should be given to fuse the target spine to be treated. It is recommended but not required that MRIs are obtained with the simulation position. MR simulation should be used where available.

6.3.1.1 Radiosurgery Target Volume

The radiosurgery target volume includes only the involved vertebral body and both left and right pedicles as shown in Figure 2 below and the grossly visible tumor, if a paraspinal or epidural lesion is present. **An epidural lesion is included in the target volume provided that there is a ≥ 3 mm gap between the spinal cord and the edge of the epidural lesion. A paraspinal mass ≤ 5 cm in the greatest dimension contiguous with spine metastasis is included in the target volume.** In this study, the terms, GTV or CTV, are not used.

The target as defined above will not be enlarged (i.e., no "margin" for presumed microscopic extension). This target volume ultimately becomes the radiosurgery planning target volume. The radiosurgery does not assume set-up errors. However, depending on

the radiosurgery system, a beam aperture margin of 2-3 mm beyond the target volume is allowed to meet the adequate dose coverage of the target. This margin can be reduced to 0-1 mm at the area of spinal cord to meet the spinal cord dose constraints. The treatment plan is acceptable as long as ≥ 90% of the target volume receives the prescribed radiosurgery dose.

Examples of radiosurgery target volumes are illustrated in Figure 2. Solid black represents the tumor that can be seen on the imaging studies.

Most of the spine metastases involve the vertebral body and the gross tumor seen on MRI or CT scan, as shown in Figure 2a below. This is the most common type of spine metastasis. The radiosurgery target volume includes the involved vertebral body and both pedicles (solid red line).

Metastatic lesions can be more extensive, involving the pedicles [Figure 2b]. The target volume can be more generous [dotted line of Figure 2b], or the target volume can include anterior and posterior elements of the spine [solid red line of Figure 2b]. The target volume may be chosen at the discretion of the treating Radiation Oncologist based on the extent of tumor involvement.

When the metastasis involves only the posterior element, the target volume includes the spinous process and laminae [solid red line of Figure 2c].

In any circumstance, when there is an epidural or paraspinal soft tissue tumor component, the visible epidural or paraspinal tumors are included in the target volume.

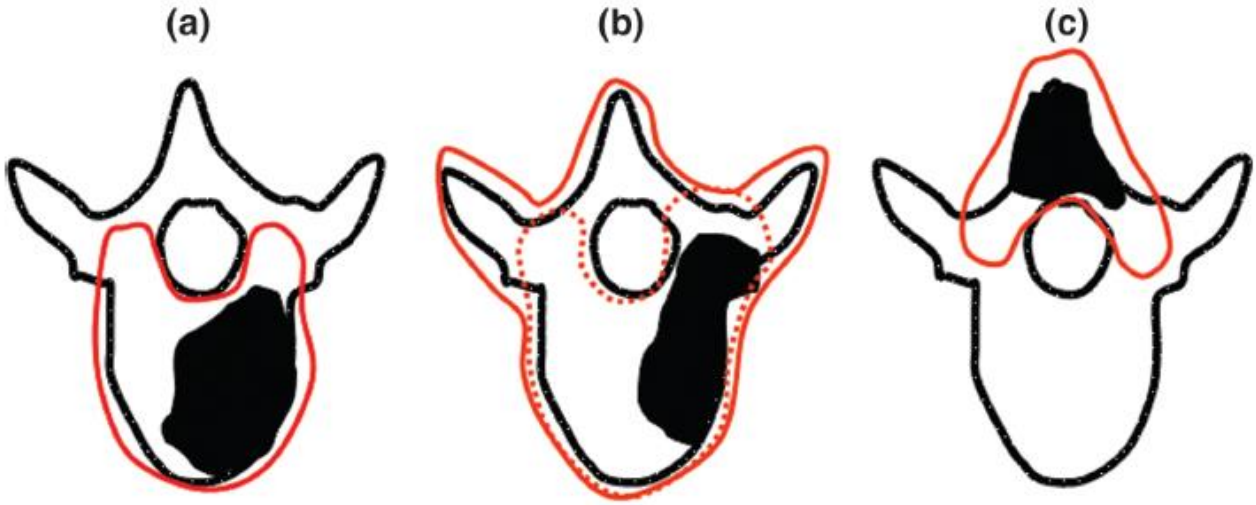


Figure 2: Diagram of Spine Metastasis and Target Volume

6.3.1.2 Spinal Cord Volume

Two spinal cord contour sets are required for this protocol: the conventional and the partial spinal cord volumes.

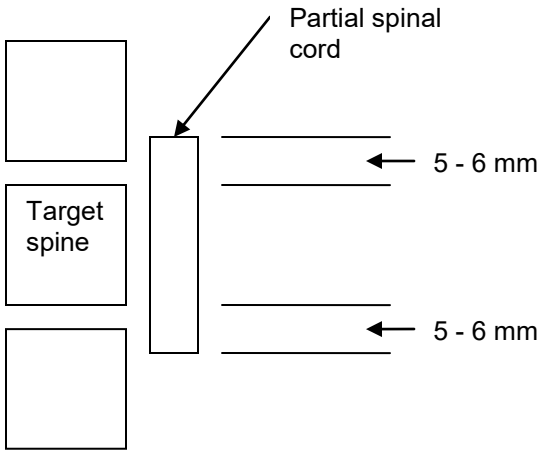
The conventional spinal cord volume is contoured on the simulation CT based on the image fusion with T2-weighted and T1-weighted MRI with contrast. It is recommended that a simulation CT be done with contrast, but this is not required. **The conventional spinal cord** should be contoured starting at least 10 cm above the superior extent of the target volume and continuing on every CT slice to at least 10 cm below the inferior extent of the target volume. This spinal cord volume is required to be consistent with image-guided radiotherapy volume definition of NRG Oncology protocols.

The partial spinal cord volume is specific to this study. The definition of partial spinal cord volume is shown in Figure 3below. The spinal cord is contoured based on the image fusion

with T2-weighted and T1-weighted MRI with contrast. It is recommended that a simulation CT image be done with contrast, but this is not required. The partial spinal cord should be contoured starting from 5-6 mm above the superior extent of the target volume to 5-6 mm below the inferior extent of the target volume. The spinal cord should be drawn on every slice of simulation CT. The variation of 5-6 mm is due to the pre-determined slice thicknesses of 2.5-3 mm by different CT manufacturers.

Three cord dose constraints are used in this study: 1) the dose constraints for the partial spinal cord is 10 Gy to no more than 10% of the partial spinal cord volume; or 2) the dose constraint for the conventional spinal cord is 10 Gy to the spinal cord volume less than 0.35cc; or 3) the maximum cord dose is 14 Gy for less than 0.03cc. These constraints are applied to the treated spine level. Any spinal cord dose exceeding these constraints is not acceptable and is a major deviation.

Figure 3: Diagram of Defining Partial Spinal Cord Volume



Radiosurgery is not recommended for any cases that do not meet the spinal cord constraints. Each CT slice within the radiosurgery plan should be checked to screen any unacceptably high radiation dose to the spinal cord at any particular slice. In this situation, the treating physician can make the decision of proceeding or stopping the radiosurgery or to perform re-planning. Critical organs including spinal cord, liver, kidneys, and lung should be analyzed for radiation dose distribution if any of them are transected by any radiation field. The dose-volume guidelines are described in Sections 6.3.2 and 6.4.

6.3.2 *Dosimetry*

Intensity-modulated radiation therapy (IMRT) or other dose painting techniques will be used to deliver highly conformal dose distributions. Non-coplanar beams can be employed. Non-opposing beams are preferable. Multiple beam directions or arcs of radiation will be used for geometrically complicated lesions. The beam arrangement should be placed mostly from the posterior direction to avoid the radiation beam entering through the lungs. Intensity-modulated arc therapy with either multiple static cones or dynamic conformal multileaf collimators (MLC) can be used. For arc rotational techniques, every effort should be used to limit the radiation through the lung.

A common point should be defined, which is close to the center of the target volume for dose normalization. Preferably, this point is placed at the treatment isocenter if a linac based delivery system is used. The plan should be normalized to the common point or isocenter or its vicinity suitable for dose normalization. Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Inhomogeneity correction must be included for dose calculation. The prescription dose of 16 or 18 Gy will be delivered to the margin of the target volume and fulfill the requirements below. The treatment plan is acceptable as long as > 90% of the target volume receives the prescribed radiosurgery dose.

Successful treatment planning will require accomplishment of all of the following criteria:

1) Prescription Isodose Surface Coverage

Patients will receive 16 or 18 Gy in 1 fraction of radiosurgery. This study requires 90% coverage of the target volume by the prescribed dose. Typically, the 80-90% isodose line is used as prescription line. Depending on the delivery system, this prescription isodose line may be different. Coverage of < 90% of the target volume is a Variation Acceptable, and any coverage of < 80% of the target volume is a Deviation Unacceptable.

2) Target Dose Heterogeneity

The treatment plan is per protocol as long as ≥ 90% of the target volume receives the prescribed radiosurgery dose. Dose inhomogeneity can exist within the target volume.

3) High Dose Spillage

Because of the irregular shape of target volume and the position of the spinal cord, there can be hot spots in the immediate vicinity outside of the target volume. The area of hot spot often can be seen in the immediate paraspinal areas or within the paraspinal muscle (e.g., psoas) or rib cage including intercostals muscle. Dose spillage is considered to be Per Protocol if the following dose limits are met. Plans that do not meet these limits are scored as either Variation Acceptable or Deviation Unacceptable (see Section 6.6.1.1).

The Per Protocol plan:

- limits dose outside of the target volume to greater than or equal to 105% of the prescription dose to a volume of less than or equal to 3.0 cc ;
- limits dose of greater than or equal to 105% of the prescription dose to a region within 1.0 cm from the edge of the target volume ;
- excludes all doses of greater than or equal to 110% of the prescription dose outside of the target volume.

It is important to point out that these dose limits do not override the dose restrictions for the spinal cord stated below in Section 4 (Spinal Cord Dose) and in Section 6.4.1.1. The high dose spillage conditions can be determined by expanding the target defined in Section 6.3.1.1 by 1 cm. Examination of the DVH for this rind around the target will determine the size of any high dose regions outside the target. If the region of dose higher than 105% of the prescribed dose is seen to go outside of this margin region, the case will be scored according to the rules in Section 6.6.1.1.

4) Spinal Cord Dose

The most important requirement is the spinal cord dose constraint 10 Gy to the 10% of the partial spinal cord volume defined as 5-6 mm above and below the target. For multiple lesions, the partial cord volume and the 10% volume will increase. In no case should the dose of 10 Gy be exceeded for a spinal cord volume of 0.35 cc. The absolute maximum dose to any part of the spinal cord will be 14 Gy for a volume of 0.03 cc. Radiosurgery should not be used for any cases with spinal cord dose exceeding the described constraints in this study. Any spinal cord dose that does not meet these criteria is a major deviation.

5) Low Dose Spillage

The falloff gradient beyond the target volume extending into normal tissue structures must be rapid in all directions and meet the following criteria: Using radiation beams directed from posterior to minimize passage of radiation through the lungs is strongly recommended.

6.4 Critical Structures (4/21/14)

Note: All required structures must be labeled as listed in the table below for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard dicom name listed.

Standard Name	***Description***	
PTV_1600	PTV is defined as only the gross tumor	Required for Rx Dose 16 Gy
NonPTV1600	External – PTV_1600	Required for Rx Dose 16 Gy
NonPTV1600_10	External – (PTV_1600+10mm)	Required for Rx Dose 16 Gy
NonPTV1600_15	External – (PTV_1600+15mm)	Required for Rx Dose 16 Gy
PTV_1800	PTV is defined as only the gross tumor	Required for Rx Dose 18 Gy
NonPTV1800	External – PTV_1800	Required for Rx Dose 18 Gy
NonPTV1800_10	External – (PTV_1800+10mm)	Required for Rx Dose 18 Gy
NonPTV1800_15	External – (PTV_1800+15mm)	Required for Rx Dose 18 Gy
PTV_800	PTV is defined as only the gross tumor	Required for Rx Dose 8 Gy
PTV_100mm	Expand PTVs by 10 cm	**Required**
Lung_L	Left Lung	Required when applicable
Lung_R	Right Lung	Required when applicable
Lungs	Total Lung	Required when applicable
Esophagus	10cm above/below the extent of PTV	Required when applicable
SpinalCord_Prt	Partial Spinal Cord volume within 5-6mm above/below the PTV	Required when applicable
SpinalCord	Normal spinal cord contour	Required when applicable
BrachialPlexus	Ipsilateral Brachial Plexus	Required when applicable
External		**Required**
Kidney_L		Required when applicable
Kidney_R		Required when applicable
Trachea		Required when applicable
Larynx		Required when applicable
Heart		Required when applicable
SkinOAR		**Required**
GreatVessels		Required when applicable
Stomach		Required when applicable
Duodenum		Required when applicable
Jejunum_Ileum		Required when applicable
Colon		Required when applicable
Rectum		Required when applicable
RenalHilum	Renal hilum/vascular trunk	Required when applicable
RenalCortex		Required when applicable
SacralPlexus		Required when applicable
CaudaEquina		Required when applicable

6.4.1 *Critical Organ Dose-Volume Limits*

The following table lists maximum dose limits to a point or volume within several critical organs recommended for stereotactic body radiation therapy (SBRT). The recommended dose constraints are shown in volume and the maximum dose to the given volume for each organ

(Timmerman 2008). **Note**: The dose to the spinal cord has been modified from the original publication.

Table 1: One Fraction Dose Constraints for Arms 1 and 2

Serial Tissue	Volume	Volume Max (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	Less than or equal to 0.35cc	10 Gy	myelitis
AND			
Spinal Cord	Less than or equal to 10% of the partial spinal cord	10 Gy	myelitis
AND			
Spinal Cord	Less than or equal to 0.03cc	14 Gy	myelitis
Cauda Equina	<0.03 cc <5 cc	16 Gy 14 Gy	neuritis
Sacral Plexus	<0.03 cc <5 cc	18 Gy 14.4 Gy	neuropathy
Esophagus*	<0.03 cc <5 cc	16 Gy 11.9 Gy	stenosis/fistula
Ipsilateral Brachial Plexus	<0.03 cc <3 cc	17.5 Gy 14 Gy	neuropathy
Heart/Pericardium	<0.03 cc <15 cc	22 Gy 16 Gy	pericarditis
Great vessels*	<0.03 cc <10 cc	37 Gy 31 Gy	aneurysm
Trachea* and Larynx	<0.03 cc <4 cc	20.2 Gy 10.5 Gy	stenosis/fistula
Skin	<0.03 cc <10 cc	26 Gy 23 Gy	ulceration
Stomach	<0.03 cc <10 cc	16 Gy 11.2 Gy	ulceration/fistula
Duodenum*	<0.03 cc <5 cc	16 Gy 11.2 Gy	ulceration
Jejunum/Ileum*	<0.03 cc <5 cc	15.4 Gy 11.9 Gy	enteritis/obstruction
Colon*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	colitis/fistula
Rectum*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	proctitis/fistula
Renal hilum/vascular trunk	<2/3 volume	10.6 Gy	malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	**Endpoint (≥ Grade 3)**
Lung (Right & Left)	1000 cc	7.4 Gy	Pneumonitis
Renal cortex (Right & Left)	200 cc	8.4 Gy	Basic renal function

*Avoid circumferential irradiation

These limits were formulated based on the widely accepted norms with radiosurgery in current practice. Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. See Section 6.4.2 for instructions for the contouring of these organs.

6.4.1.1 The spinal cord dose constraints are partially based on the previous published data (Ryu 2008, Timmerman 2008). See Sections 6.3.1.2 and 6.3.2 for further details of the spinal cord dose.

6.4.1.2 The lung dose constraint is based on a critical volume model and requires no more than 1,000 cc of lung tissue to be treated to a dose ≥ 7.4 Gy. Since the prescribed dose is only 16 or 18 Gy, V20 as a single dose does not exist in this trial.

6.4.2 *Contouring of Normal Tissue Structures*

Normal tissue contouring is required starting at 10 cm above the target volume to 10 cm below the target.

6.4.2.1 Spinal Cord

Two spinal cord contour sets are required for this protocol: the conventional and partial spinal cord volumes. See Section 6.3.1.2 for details.

6.4.2.2 Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and muscular layers. The esophagus should be defined starting at least 10 cm above the superior extent of the target volume and continuing on every CT slice to at least 10 cm below the inferior extent of the target volume.

6.4.2.3 Larynx and Pharynx

The larynx and pharynx will be contoured to the mucosal, submucosa, and cartilages and airway channels associated with these structures.

6.4.2.4 Trachea and Airway

The trachea and airway adjacent to the spines will be contoured including the mucosal, submucosa and cartilage rings and airway channels.

6.4.2.5 Lung

Both the right and left lungs should be contoured using pulmonary windows. All inflated and collapsed lung should be contoured; however, paraspinal gross tumor, if any, should not be included in this structure.

6.4.2.6 Kidney

Both the right and left kidneys should be contoured. Paraspinal gross tumor as defined above should not be included in this structure.

6.4.2.7 Skin

The skin will be defined as the outer 0.5 cm of the body surface. As such, it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

6.5 Documentation Requirements (8/30/11)

6.5.1 In general, treatment interruptions (e.g. due to intractable pain during the treatment) should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record. For Arm 1 patients, IGRT data must be submitted; see Section 6.6.2 for details.

6.6 Compliance Criteria for Arm 1 Spine Radiosurgery (8/30/11)

6.6.1 *Dosimetry Compliance*

Section 6.0 describes appropriate conduct for treatment planning dosimetry. The optimal target coverage level is ≥ 90% volume to be covered by the prescription dose. Coverage of < 90% is a Variation Acceptable, and coverage of < 80% is a Deviation Unacceptable. Any spinal cord dose exceeding the dose constraint in Section 6.3.1.2 is not acceptable and is a major deviation. The table in Section 6.4 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor violation. Exceeding these limits by more than 5% constitutes a major deviation.

6.6.1.1 High Dose Spillage

Per Protocol plan

- limits dose outside of the target volume to greater than or equal to 105% of the prescription dose to a volume of less than or equal to 2.0 cc;
- limits dose of greater than or equal to 105% of the prescription dose to a region within

1.0 cm from the edge of the target volume;

Variation Acceptable is defined by any one of the following

- allows doses outside of the target volume that are greater than or equal to 105% of the prescription dose to occupy a volume that is greater than 2.0 cc but does not exceed 3.0 cc;
- allows doses outside of the target volume that are greater than or equal to 105% of the prescription dose to extend beyond 1.0 cm but less than 1.5 cm from the edge of the target volume;
- allows doses outside of the target volume to go above 110% but not above 115% of the prescription dose.

Deviation Unacceptable is defined as any dose distribution where the limits stated for Variation Acceptable are not met.

6.6.2 *IGRT: Treatment Delivery Compliance*

Pre-treatment imaging, pre-treatment/post-shift imaging (if applicable), and Post-treatment imaging, including a completed IGRT spreadsheet of the shifts, are REQUIRED to be obtained and submitted.

Setup images (obtained from the IGRT system) will be compared to corresponding reference images to identify any potential deviation. The institution's IGRT systems must demonstrate < 2 mm agreement between simulation/planning and treatment, as well as at the end of treatment.

6.7 R.T. Quality Assurance Reviews (11/22/13)

The Principal Investigator, Samuel Ryu, MD, and his Co-Chairs will perform a rapid review of the treatment plan for the first 2 cases from each institution prior to the institution delivering any protocol treatment using radiosurgery/SBRT. Institutions should allow 3 business days for this initial case to be received, processed, and reviewed. If the plan must be resubmitted, it will be given a rapid review as described in Section 6.0. Treatment plans for subsequent patients enrolled at a site will not be reviewed prior to delivery of treatment, but a review will be performed at a later date to evaluate protocol compliance.

Treatment planning images and dosimetry planning information in accepted format will be submitted to TRIAD for quality assurance (QA) purposes in all cases. See Section 12.2 for data submission.

It is recommended that each institution have a policy of quality assurance according to the guideline of SBRT by ASTRO and ACR (Potters 2004; Bissonnette 2007; Yoo 2006). The standard practice of checking radiation output should be carried out each day of treatment. Tests aimed at guaranteeing agreement of the image guidance system and the treatment system, including repositioning accuracy, must be carried out each day an SBRT treatment is scheduled. Dose delivery must be carried out for these treatments.

The Study Chair, Samuel Ryu, MD, and the Medical Physics Co-Chair, Dr. Yin, will perform an RT Quality Assurance Review on an ongoing basis. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at IROC Phila RT, whichever occurs first.

Participating institutions must have a QA for spine radiosurgery based on the site's radiosurgery method and equipment. The following can be used as a guideline. Detailed QA information can be found in the AAPM TG 142 report.

Daily Stereotactic System QA

1. Linac morning warm up and radiation output check;
2. Localization system (mainly immobilization and imaging systems) QA, including the geometric alignment of the imaging system and delivery system;
3. Linac isocenter accuracy QA, mainly checking the stability during gantry rotation and table rotation and the consistency of the room laser system with the Linac isocenter.

Individual Patient QA

1. Dose calculation check;
2. Fluence/map field check for IMRT;
3. Collision check for each treatment field;
4. Patient position setup and check.

6.8 EXTERNAL BEAM RADIATION THERAPY, PHASE III COMPONENT, ARM 2 (8/30/11)

INTENSITY MODULATED RADIOTHERAPY (IMRT) IS NOT ALLOWED FOR ARM 2 IN THE PHASE III COMPONENT OF THE STUDY.

6.8.1 Dose Specifications

6.8.1.1 *Dose Fractionation and Treatment Volume for 2D or 3D Treatment*

For Arm 2, external beam radiotherapy, the prescribed dose is 8 Gy in 1 fraction. Treatment volume will include the entire vertebral body(s) of the involved index spine, plus one vertebral body superior and one vertebral body inferior to the index spine. A treatment field margin of 1-2 cm laterally beyond the vertebral body(s) can be used, based on the treating physician's discretion, and either 2D or 3D conformal therapy is allowed at the treating physician's discretion.

6.8.1.2 *Physical Factors*

External beam radiotherapy must be given using megavoltage equipment with 4-18 MV photons. Electrons, protons, Gamma Knife® or Perfexion™ treatment are not permitted.

6.8.1.3 *Premedications*

No premedications are necessary.

Pain control to help position the patient for the purpose of treatment (not for long-term pain control) is permitted to decrease patient movement due to pain. Note: Narcotics can be used or increased for the purposes of patient positioning for radiosurgery, as clinically necessary; however, the patient should return to the prior level of pain medication after radiosurgery.

If it is necessary to minimize patient's anxiety about the treatment and disease condition or for immobilization purposes, medications such as alprazolam or lorazepam are allowed.

No steroid premedication is indicated, and it is recommended that all patients receiving corticosteroids begin tapering them immediately after external beam treatment.

6.8.2 Patient Positioning and Simulation

6.8.2.1 *Patient Positioning*

Patients must be positioned in a stable supine position at the treating physician's discretion. Any immobilization techniques can be used for conventional radiotherapy or 3D conformal therapy at the treating physician's discretion. For cervical spine or cervicothoracic junctional areas, a head and neck immobilization device can be used.

6.8.2.3 *Simulation*

Simulation of treatment fields is required prior to the treatment. There must be an acceptable DRR or simulation image and portal image documenting that the treatment site is adequately covered and verified by the treating Radiation Oncologist. Both digital and analog format images are acceptable, preferably digital images.

6.8.3 Treatment Planning

6.8.3.1 *2D Treatment*

Treatment target volume will include the involved index spine, plus one spine level superior and one spine level inferior to the index spine. A treatment field margin of 1-2 cm laterally beyond the vertebral body(s) can be used, based on the treating physician's discretion.

Field arrangements to treat the target lesion may be chosen at the discretion of the treating Radiation Oncologist. In general, posterior only, anterior-posterior, opposed lateral (for c-spine tumors), or posterior oblique field arrangements will be used. Either a SAD or SSD technique is acceptable. The treatment depth is set at the center of the spinal canal, as determined on the simulation CT or MRI or lateral film of conventional simulation.

Anterior and posterior parallel opposed fields can be used for thoracic or lumbar spine. Equal or unequal weighting may be used (e.g., a ratio of doses of 1:2 AP:PA). The dose is prescribed to the center of the spinal canal of the involved index spine.

Parallel opposed lateral fields can be used for cervical spine. When lateral fields are used, the isocenter should be at mid-thickness, with the dose prescribed to the center of the spinal canal.

The prescription point is set at the center of the spinal canal of the involved index spine, as determined on the simulation CT or MRI or anterior/lateral films of conventional simulation. Dose is prescribed to a point, not the treatment volume. While dose is prescribed to a point, it is recommended (but not required) that the goal of appropriate treatment planning aim to achieve coverage of the target lesion volume by at least 90% of the prescribed dose. Three-dimensional conformal therapy is allowed, but IMRT is not allowed for Arm 2.

6.8.3.2 *3D Treatment*

CT simulation is required. Treatment volume will include the entire vertebral body(s) of the involved index spine, plus one vertebral body superior and one vertebral body inferior to the index spine. Non-coplanar beams can be employed. Multiple beam directions can be used.

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

A common point should be defined, which is close to the center of the target volume for dose normalization. Preferably, this point is placed at the treatment isocenter if a linac-based delivery system is used. The plan should be normalized to the common point or isocenter or its vicinity suitable for dose normalization. Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Inhomogeneity correction must be included for dose calculation. The prescription dose will be delivered to the margin of the target volume. The treatment plan is acceptable as long as more than or equal to 90% of the target volume receives the prescribed dose, with the same normal tissue constraints described in Table 1. Dose inhomogeneity can exist within the target volume.

6.8.4 Critical Structures

See Section 6.4.1, Table 1, "One Fraction Dose Constraints for Arms 1 and 2".

For 2D treatment, contouring of normal tissue structure is not required. However, spinal cord dose should be recorded at the point of dose prescription, i.e., at the center of the spinal canal. Normal tissue structures can be delineated and the dose can be recorded at the treating physician's discretion. Any adverse events should be reported as described in Section 6.10.

For 3D treatment, the same normal tissue constraints described in Table 1 apply. The normal tissues as well as the target volume should be delineated as described in Section 6.3.1.2. If the normal tissue constraints are not met at the 10 Gy level, the total dose can be lowered to 8 Gy at the treating physician's discretion. Any adverse events should be reported as described in Section 6.10.

6.8.5 Documentation Requirements

6.8.5.1 For 2D treatment, portal images of each field must be obtained on or before the day of therapy but sites are not required to submit these.

6.8.5.2 Planning images and dosimetry information for 2D treatment are not required to be submitted.

6.8.5.3 Isodose plans and documentation of isocenter positions for 3D radiotherapy are required to be submitted per Section 12.2.

6.8.5.4 In general, treatment interruptions (e.g., due to intractable pain during the treatment) should be avoided by preventative medical measures. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.8.6 Compliance Criteria for 3D Treatment

Dosimetric compliance for the protocol is that coverage of < 90% but ≥ 80% of the target volume is a Variation Acceptable, and any coverage of < 80% of the target volume is a Deviation Unacceptable.

EBRT will follow the normal tissue dose constraints as shown in Section 6.4, Table 1. Exceeding these limits by more than 2.5% constitutes a minor violation. Exceeding these limits by more than 5% constitutes a major deviation.

6.8.7 Compliance Criteria for 2D Treatment

The treatment chart, including the prescription page, must be submitted. Treatment planning information and portal images of each field must be obtained on or before the day of therapy, will be archived at the site and will only be submitted if requested.

6.9 Radiation Therapy Adverse Events

6.9.1 *Radiation Myelitis*

Given the proximity and position of spinal cord in relation to the radiosurgery target, every effort should be made to minimize the radiation dose to the spinal cord. Radiation myelitis is a subacute or chronic clinical syndrome after radiation. The symptoms may include paresthesia, sensory changes, and motor weakness including paralysis. There is no active treatment for radiation myelitis; therefore, it is important to prevent any injury to the spinal cord. Corticosteroids are used when clinical symptoms develop.

In the Henry Ford Hospital experience, one case of radiation myelitis was reported.(Ryu 2007). The patient had a diagnosis of invasive breast cancer. The initial treatment was mastectomy followed by chemotherapy (cyclophosphamide, methotrexate, and fluorouracil). After 9 years, she developed recurrence at the chest wall and was treated with radiotherapy and then continued hormonal therapy. After another 6 years, she presented to our institution with voice change due to vocal cord paralysis and difficulty in swallowing. MRI showed contrast enhancing mass involving the clivus, occipital condyles, and C1 vertebra with epidural compression. This was consistent with metastatic involvement. She was treated with single dose radiosurgery 16 Gy, prescribed to the 90% isodose line encompassing the gross tumor volume. The same spinal cord dose constraints described above were used. The doses to the spinal cord volume of 30%, 20%, 10%, 5%, and 1% were 6.2 Gy, 7.6 Gy, 9.6 Gy, 11.1 Gy, and 13.0 Gy, respectively. The maximum point dose to the spinal cord in this patient was 14.6 Gy, which was even lower than the average maximum of other patients. The spinal cord volume within the 80% isodose line was 0.06 cc, and 0.32 % cord volume. The patient had a complete neurologic recovery and pain relief, and a complete tumor response radiographically. She then received chemotherapy with carboplatin and docetaxel for 6 months and continued trastuzumab as well as zoledronic acid and fulvestrant (at another institution). However, 13 months after radiosurgery, she developed right lower extremity weakness with 4/5 muscle strength. There was no sensory deficit. MRI revealed T2 signal abnormality in the cervicomedullary junction at the level of radiosurgery target, and contrast enhancement in the ventral aspect of medulla and right cerebellum. These changes appeared to be consistent with radiation effect. She was treated with dexamethasone and had symptom improvement. This patient did not have any other comorbidities or other metastatic progression.

6.9.2 *Radiation Esophagitis*

Patients with thoracic spine treatment will likely develop esophageal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. There are no long-term adverse events reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal esophagus. The consequences of esophageal toxicity, e.g., swallowing difficulty, dysphagia, cough, dehydration, and fistula, should be documented.

In the Henry Ford Hospital experience, one case of tracheoesophageal fistula was reported in patient with multiple myeloma (Ryu 2008b). This patient was severely immunocompromised from previous bone marrow transplantation and systemic chemotherapy with multiple medical comorbidities including a mycobacterial granulomatous infection involving the esophagus. The patient was treated for spinal cord compression at T4 and paraspinal mass with a dose of 16 Gy. The patient had excellent tumor response but later developed a tracheoesophageal fistula at the treated site. Biopsy also revealed granulomatous infection. It was believed that radiation contributed, at least in part, to the development of the fistula.

6.9.3 *Radiation Laryngitis or Pharyngitis*

Patients with cervical spine treatment will likely develop laryngopharyngeal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment

including hydration is advised. No long-term laryngopharyngeal toxicity has been reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal larynx and pharynx. The consequences of toxicity, e.g., swallowing difficulty, dysphagia, cough, dysphonia dehydration, and fistula, should be documented.

6.9.4 *Tracheal Injury*

Although no cases of tracheal injury have been reported with spine radiosurgery, it is prudent to minimize the radiation spillage in the normal trachea. The consequences of tracheobronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should be documented.

6.9.5 *Radiation Pneumonitis*

There have been no reported cases of symptomatic radiation pneumonitis with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the lung tissue. It is strongly recommended to use radiation beams directed from posterior to avoid passage of radiation through the lungs.

Patients with symptoms of pneumonitis will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with non-steroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immuno-compromised patients.

6.9.6 *Compression Fracture of Treated Vertebra*

There has been no formally reported incidence of vertebral compression fracture as the result of spine radiosurgery; the incidence is estimated to be 5-30% (Jin 2006; Yamada 2008). Patients with multiple myeloma appear to be more prone to develop compression fracture than patients with other histology. There is no known radiation dose relationship. This study is designed to follow up the potential bony change of the treated spine by imaging studies. The most common symptom from compression fracture is pain. Kyphoplasty or vertebroplasty can be used to address the compression fracture; however, retropulsed compression causing neurological signs may need surgery.

6.9.7 *Other Adverse Events*

Short-term or long-term injury to the kidney or upper airway has not been reported. If other severe adverse events occur, details should be documented.

6.10 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements (09/23/16)

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the CTEP Adverse Event Reporting System (CTEP-AERS) application as directed in this section.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for routine adverse event (AE) reporting on the case report form.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS. CTEP-AERS utilizes the NCI CTCAE version 4.0 and the application can be accessed via the CTEP web site
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1389817585865

All appropriate treatment areas should have access to both the CTCAE versions 3.0 and 4.0. . The CTCAE versions 3.0 and 4.0 are located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

Routine adverse event reporting guidelines are available at (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx).

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.
Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table below will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below. **Contact the CTEP-AERS Help Desk if assistance is required.**

AdEERS REPORTING REQUIREMENTS

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1389817585865

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection

- AdEERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. For instructions to submit supporting documentation, , contact NRG Oncology at 1-215-574-3191**.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via A CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials:

The following are protocol-specific exceptions to expedited reporting via CTEP-AERS: grade 1 and grade 2 adverse events. Routine adverse event reporting on the case report form fulfills safety reporting requirements for these events during protocol treatment.

6.10.1 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via CTEP-AERS within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

8.1 *Spine Instability and/or Compression Fractures*

Patients with overt spinal instability or direct spinal cord or *cauda equina* compression, particularly with bony retropulsion, should be evaluated by a qualified spine surgeon for possible open surgical intervention. These patients are not eligible for this study. The decision for open surgical intervention will be determined by the institution's treating neurosurgeon and radiation oncologist.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 *Steroids*

Prophylactic use of steroids is not necessary. No steroid premedication is indicated for radiosurgery treatment. If the patient has already started steroid medication, it can be tapered immediately after radiosurgery is completed (see Section 6.1.3).

9.1.2 *Analgesics*

Pain control to help position the patient for the purpose of treatment (not for long-term pain control) is permitted to decrease voluntary patient movement. **Note: Narcotics can be increased for the purposes of patient positioning for treatment, as clinically necessary for pain control** (see Section 6.1.3).

9.1.3 *Anti-Anxiety Medications*

If it is necessary to minimize patient's anxiety about the treatment and disease condition or for immobilization purposes, medications such as alprazolam or lorazepam are allowed for the radiosurgery procedure.

9.1.4 *Supportive Therapy for Acute Radiation Reactions*

Supportive therapy is allowed for medical care of acute radiation symptoms, such as treatment of mucositis.

9.2 Non-permitted Therapy

Chemotherapy is not permitted within 24 hours prior to or concurrently with radiosurgery. In addition, the patient can receive chemotherapy no earlier than 24 hours after radiosurgery.

10.0 SPECIMEN SUBMISSION — Phase III Component Of The Study (09/23/16)

For patients who have consented to participate in the specimen submission component of the study (See the Sample Informed Consent).

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as specimen submission. If the patient consents to participate in the specimen component of the study, the site is required to submit the patient's specimens as specified below. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

10.1 Specimen Submission (09/23/16)

The NRG Oncology Biopspecimen Bank-San Francisco at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. NRG Oncology encourages participants in protocol studies to consent to the banking of their specimens. The NRG Oncology Biopspecimen Bank provides specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. **Note**: The NRG Oncology Biopspecimen Bank will provide collection kits and instructions at no charge for the submission of specimens in this protocol; see Appendices IV and V.

In this study, it is strongly encouraged that blood (serum/plasma/whole blood) and urine be submitted to the NRG Oncology Biopspecimen Bank for the purpose of banking and for translational research. If the patient consents, serum, plasma, whole blood, and urine will be collected at baseline and serum, plasma, and urine at 3 months from randomization.

We will explore promising biomarkers to date with regard to side effects from treatment. Although substantial evidence has been obtained from a series of studies suggestive of a genetic basis for clinical radiosensitivity of normal tissue, much work still remains to be accomplished in this area.

The whole blood collected will be utilized for single nucleotide polymorphisms (SNPs). Single nucleotide polymorphisms (SNPs) are the most common variation responsible for genetic diversity between individuals, accounting for more than 85% of the variability. Recent advances in SNP identification and analysis have made SNP genotyping an invaluable tool to examine the variations responsible for disease susceptibility and radiation responsiveness. SNP genotyping applications have recently extended into personalized health care.

The pretreatment plasma, serum and urine and 3 month post-treatment collection of these fluids will be tested for a number of cytokines and proteins that are thought to be predictive of long-term radiation toxicity. This may lead to identification of promising similar or new biomarkers with the goals of

1. Identifying factors predictive of outcome such that patients may be better stratified in future trials;
2. Developing novel treatment strategies which target the molecular abnormalities identified.

10.2 Specimen Collection for Translational Research and Tissue Banking (09/23/16)

For patients who have consented to participate in the tissue/blood component of the study. See Appendix IV for urine and blood collection kits and detailed collection instructions. Collection kits with one pre-paid shipping label per case can be requested from NRGBB@ucsf.edu. Batch

shipping all samples from each case in one shipment is requested for this trial. As the effects of many specimen processing parameters on the measurements of biomarkers is unknown, please follow the instructions in the appendix carefully and record processing information as requested. Any deviations from the instructions should be recorded but may make a specimen unbankable.

10.2.1 Blood Sample Preparation

20-30 ml peripheral blood (Two 10 ml EDTA tubes and one 10ml Red-top tube) will be taken from each individual before treatment and 20 mls (one 10 ml EDTA tube and one 10ml red-top tube) at 3 months from randomization. Use sterile techniques to avoid contamination.

See Appendix IV for detailed instructions on kit requests, collection, processing, storage and shipping. (**Note**: if the site misses the pre-treatment collection time point then the site may collect whole blood at any time point or follow-up visit but this must be noted on the Specimen Transmittal Form)

10.2.2 The following materials must be provided to the NRG Oncology Biopspecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG Oncology protocol number; the patient's case number; the collection time point, and method of storage, for example, stored at -80° C, must be included.

10.3 Storage Conditions (8/30/11)

Store at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

10.4 Specimen Collection Summary (09/23/16)

Specimens taken from patient:	Collected When:	Submitted as:	Shipped:
Plasma: 5-10 mL of whole blood in EDTA tube #1 (purple/lavender top) and centrifuge per Appendix IV	1) Pre-Treatment 2) 3 months from randomization	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (5 vials)	Plasma sent frozen on dry ice via overnight carrier (ship Mon-Wed only) Batch ship whole case in one shipment or with other cases.
Serum: 5-10 mL of whole blood in Red-top tube and centrifuge per Appendix IV	1) Pre-Treatment 2) 3 months from randomization	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (5 vials)	Serum sent frozen on dry ice via overnight carrier (ship Mon-Wed only) Batch ship whole case in one shipment or with other cases.
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix per Appendix IV	Pre-treatment. (Note if site misses this collection time point site may collect whole blood at any time point or follow-up visit but must note this on the Specimen Transmittal Form).	Frozen whole blood samples containing 1 ml per aliquot in 1 ml cryovials (3 to 5 vials)	Whole blood sent frozen on dry ice via overnight carrier (ship Mon-Wed only)
10-15 mL clean-catch urine	1) Pre-Treatment 2) 3 months at randomization	5-10 ml unpreserved urine aliquotted into one- two sterile 15 ml polypropylene tubes.	Urine sent frozen on dry ice via overnight carrier (ship Mon-Wed only)

			Batch ship whole case in one shipment or with other cases.

10.5 Submit materials for Banking and Translational Research as follows: (09/23/16)

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143

Courier Address (FedEx, UPS, etc.): For Trackable FFPE and ALL Frozen Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.6 Reimbursement (4/14/15)
NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new National Clinical Trials Network (NCTN) Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system.

10.7 Confidentiality/Storage (12/1/09)
(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.7.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biopspecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.7.2 Specimens for banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS (09/23/16)

11.1 Study Parameters: See Appendix I for a summary of patient assessments and timeframes.

11.2 Evaluations: Phase III Component (09/23/16)

11.2.1 The patient will complete the Numerical Rating Pain Scale (NRPS) documenting the worst pain of treated spine lesion(s) at the baseline clinic visit (on the day of treatment) and at home at 1, 2, and 3 weeks after randomization and will record their pain medications and any side effects they are experiencing. Documentation of the patient's initial pain score is required.

Sites will make 3 copies of the NRPS (available on either the **I1** or **F1** forms) for the patient to complete at home at these time points, and patient will bring in the NRPS and record of pain medications and side effects at the clinic visit 1 month after randomization. At this clinic visit, patients will complete the 1 month NRPS on the same day of the week as the patient's

treatment occurred, and sites will summarize the patient's pain level, pain medications, and document any adverse events on the **F1** form (see Section 12.1). Patients also will complete the NRPS at the 3 (required), 6, 12, and 24 month clinic visits. The physician may ask this question of the patient during the visit and record the pain score in the patient's chart rather than having the patient complete the NRPS on paper.

The NRPS score should be collected for each spinal metastasis site treated. The highest numerical pain score of the index lesion will be followed for the primary endpoint of pain response (i.e., improvement at this treated site of ≥ 3 points on the NRPS, as long as other sites remain stable or decrease). If there is more than one site with identical highest pain score, then the most cephalad lesion will be defined as the index lesion.

The NRPS is an 11-point scale (0-10). Patients are instructed that 0 indicates no pain and that 10 indicates the worst pain imaginable. In general, scores of 1-4 indicate mild pain, scores of 5-6 indicate moderate pain, and scores of 7-10 indicate severe pain. Patients will be instructed to report the pain score of each treated site. Patients can complete the NRPS in approximately 1 minute.

11.2.2 An MRI of the treated spine will be obtained at baseline and at 3, 6, 12, and 24 months after randomization to assess the paravertebral or epidural tumor response as well as the subacute or long-term change of vertebral bone after radiosurgery.

11.2.3 Quality of Life Assessments

Patients participating in the phase III component and who agree to participate in the quality of life component of the study will complete the quality of life assessments at baseline and at 3, 6, 12, and 24 months after randomization.

NOTE: Patients must be offered the opportunity to participate in the quality of life component of the study. Sites are not permitted to delete the quality of life component from the protocol or from the sample consent.

11.2.3.1 *The Functional Assessment of Cancer Therapy-General (FACT-G)*

The FACT-G is a commonly used tool measuring general quality of life across 4 scales: physical well being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well being (7 items). It has been written at the 4th grade reading level, and patients can complete the FACT-G in 5-10 minutes. The FACT has been translated into 26 languages, and translations are accessible at the FACIT web site, http://www.facit.org/FACITOrg/Questionnaires

11.2.3.2 *The Brief Pain Inventory (BPI)*

The BPI asks patients to rate their pain for the last week on 0-10 scales. Patients also are asked to rate how their pain interferes with their quality of life (QOL). In addition, patients are asked to estimate the pain relief they receive from their pain treatment. The patient can complete the BPI in approximately 5 minutes. The BPI has been validated in 12 languages. Translations can be accessed at https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html; click on "symptom assessment tools". If a translation is used, the site must transcribe the data to the appropriate NRG Oncology data form and attach the patient's original.

11.2.3.3 *The EuroQol (EQ-5D)*

The EuroQol (EQ-5D) is a two-part questionnaire that the patient can complete in approximately 5 minutes. Note: The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at http://www.euroqol.org/. The site research nurse or CRA should encourage the patient not to skip questions on the EQ-5D or take breaks during the completion of this questionnaire, as this will invalidate the assessment. If this occurs, sites will document it on the Health Utility Measurement (HP) form.

11.3 Pain Response Definitions (also see Section 13.4.1)

Pain response will be defined as follows:

11.3.1 Complete response: Post-treatment pain score of 0 at the index site;

11.3.2 Partial response: Post-treatment improvement of at least 3 points at the index site;

11.3.3 Stable response: Post-treatment pain score within 2 points of the initial pain score at the index site;

11.3.4 Progressive response: A post-treatment increase of at least 3 points at the index site.

11.3.5 A complete, partial, or stable response at the index site requires no increase in narcotic pain medication and no increase in pain score at the secondary treated site(s). Although complete response is the best possible outcome, partial response is also a satisfactory outcome. Therefore, patients with complete or partial response will be considered responders. Any patient with a complete or partial response at the index site but a progressive response at the secondary sites will be considered a non-responder.

11.4 Criteria for Discontinuation of Protocol Treatment (5/1/12)

11.4.1 Protocol treatment is discontinued when there is systemic or local progression of disease resulting in hospice enrollment. If the patient is unable to have follow-up imaging studies, clinical examinations, neurologic exams, the institution should contact Data Management for instructions.

12.0 DATA COLLECTION

Data should be submitted to:
NRG Oncology*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (8/14/15)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** with NRPS	Within 2 weeks of study entry (Phase II and Phase III components)
The Functional Assessment of Cancer Therapy-General (FACT-G) **[FA] †**	Within 2 weeks of study entry
The Brief Pain Inventory (BPI) **(QL) †**	
The EuroQol (EQ-5D) **[HP] †**	
Adverse Event Form **(AE)**	At 1 and 3 months post-study entry (Phase II component) **Note**: If no AEs to report, submit a Communication Memo (CM) for suppression.
Follow-up Form **(F1)** with NRPS**†**	At 1, 3 (NRPS-required at 3 months), 6, 12, and 24 months post-study entry
The Functional Assessment of Cancer Therapy-General (FACT-G) **[FA] †**	At 3, 6, 12, and 24 months post-study entry
The Brief Pain Inventory (BPI) **(QL) †**	
The EuroQol (EQ-5D) **[HP] †**	

† For Phase III component only

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.3) (8/14/15)

Item	Due
Preliminary Dosimetry Information (DD)	
†Digital Data Submission – Treatment Plan submitted to TRIAD exported from treatment planning system	Within 1 week post-radiosurgery & 3D-

Digital data submission includes the following: • DICOM CT, DICOM Structures • DICOM Plan • DICOM Dose • All required structures **MUST** be labeled per the table in Section 6.4. • *The "RTOG 0631 Datasheet" is available in the Forms section of the of the NRG Oncology/RTOG web* site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0631. Submit the Data Sheet via TRIAD with the digital data listed above.	CRT external beam (see Section 6.0 for details on rapid review of cases on Arm 1)
Upon submission of the digital data via TRIAD, complete an online digital data transmission form (DT) located in the Forms section on the NRG Oncology/RTOG web site at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0631	
Note: All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.	
Modified digital patient data as required submitted to TRIAD	
IGRT Submission (Arm 1 Only)	
IGRT images obtained on the day of treatment **(IG) See Section 6.6.2 for time points Submit to TRIAD. Must be DICOM or JPEG format**	Within 1 week post-radiosurgery
† IGRT Data Collection Spreadsheet on Set-up Variances **[SG] submitted via TRIAD along with the images.**	
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	
Modified digital patient data as required submitted to TRIAD select "*append"* in TRIAD	
Final RT DATA	
Radiotherapy Form (T1) Via the web	Within 1 week of RT end
Treatment Record (T5) submitted to HQ address at the top	

NOTE: For 2D cases, DRRs and portal images will be archived at the site and will only be submitted if requested.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (09/23/16)

13.1.1 Primary Endpoint

13.1.1.1 *Phase II Component*

Successful delivery of image-guided radiosurgery/SBRT in the NRG Oncology setting

13.1.1.2 *Phase III Component*

Complete or partial pain response at 3 months after study entry, as measured by the NRPS

13.1.2 Secondary Endpoints (Phase III Component)

13.1.2.1 Rapidity of pain response, defined as time from study entry to complete or partial pain relief;

13.1.2.2 Duration of pain response, defined as time from complete or partial pain relief to pain worsening (≥ 3 points);

13.1.2.3 Adverse events based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0;

13.1.2.4 Long-term effects (24 months) of on vertebral bone (compression fracture) and spinal cord;

13.1.2.5 Overall quality of life, as measured by Functional Assessment of Cancer Therapy (FACT-G); pain, as measured by the Brief Pain Inventory (BPI); and health utilities, as measured by the EuroQol (EQ-5D);

13.1.2.6 Collection of serum, plasma, buffy coat cells, and urine for future translational research.

13.2 Sample Size (6/27/14)

13.2.1 Phase II Component Sample Size Derivation

The sample size calculations for the phase II component will address the specific primary hypothesis that multiple NRG/RTOG institutions can successfully treat spine metastases with image-guided radiosurgery/SBRT. Thus, accrual from the Principal Investigator's institution, Henry Ford Hospital, will be limited to 5 patients. Treatment compliance will be deemed as acceptable, marginally acceptable with minor deviation, or unacceptable with major deviation as detailed in Section 6.0. Successful treatment will include acceptable or marginally acceptable treatment reviews. Based on the results of NRG Oncology RTOG 0236, in which 85% of patients were successfully treated with SBRT for lung cancer, we expect a similar success rate for SBRT in the spine metastases population. A success rate below 70% is unacceptable for continuation to the phase III component. Based on the one-sided exact binomial test with alpha 0.10, 41 patients would be required to detect an 18% relative reduction in the success rate (from 85% to 70%) with a statistical power of 0.85. Adjusting by approximately 5% to allow for patients that are found retrospectively ineligible, **the total sample size required for the phase II component is 43 patients**.

13.2.2 Phase III Component Sample Size Derivation

The phase III component will be pursued after establishing treatment feasibility in the phase II component. The sample size calculations for the phase III component will address the specific primary hypothesis that the use of image guided radiosurgery/SBRT (Arm 1) will result in a statistically significant improvement in pain relief at 3 months as compared to the use of external beam radiation (Arm 2), based on the Numerical Rating Pain Scale (NRPS).

The proportion of patients experiencing pain relief at 3 months after randomization will be of interest. We expect that patients treated with external beam radiation (Arm 2) will have response rates similar to those evidenced in NRG Oncology RTOG 97-14 (Section 13.2.2.1). In the subgroup of patients treated for spine metastases in NRG Oncology RTOG 97-14, 51% of patients experienced partial or complete pain relief at 3 months post-treatment. We hypothesize that image-guided radiosurgery/SBRT (Arm 1) will result in a statistically significant improvement in the proportion of patients experiencing pain relief 3 months after randomization:

$$H_0: p_1 = p_2 \text{ vs. } H_A: p_1 > p_2$$

where p_i is the proportion of patients experiencing pain relief in arm i.

Based on the one-sided exact binomial test with alpha 0.025 and a 2:1 randomization scheme, 228 patients would be required to detect a 40% improvement in the response rate (from 51% to 70%) due to image-guided radiosurgery/SBRT (Arm 1) with a statistical power of 0.80. Assuming a 5% ineligibility rate, a death rate of 15%, and a patient non-compliance rate of 15%, **the total sample size required for the phase III component would be 352 patients.**

13.2.2.1 *Stratification and Randomization*

Patients will be stratified in the phase III component according to the number of spine metastases treated (1 vs. 2) and the tumor type (radioresistant [soft tissue sarcoma, melanoma, and renal cell carcinoma] versus other types). The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution. Within each stratum, patients will be randomized in a 2:1 ratio to either image-guided radiosurgery/SBRT or external beam radiation. The 2:1 randomization allocation will be used to accommodate increased demand for image-guided radiosurgery/SBRT.

13.3 Patient Accrual

Most of the more than 570,000 people in the U.S. who die of cancer each year have tumor metastases (Jemal 1979). Bone is the third most common site of metastasis. The spine is certainly a common site. (Black 1979) There is an increasing trend of more frequently diagnosing patients with localized spine metastases because of longer survival by effective combined modality treatment, although the incidence of solitary spine metastasis is not known. There is an emerging role for image-guided radiosurgery in the treatment of localized spinal metastasis. There are no competing cooperative trials at this time.

RTOG 97-14 accrued an average of 17.1 bone metastases patients per month. Limited to patients with spine metastases, average accrual was 5.6 patients per month. Accrual to RTOG 0631 is expected to be comparable to accrual for RTOG 9714 spine metastases patients. We

project that the accrual of RTOG 0631 during the first 6 months will be negligible, in part due to the process of IRB approval and the credentialing process which will be performed in cooperation with IROC Houston. Since the credentialing process will include actual irradiation of a spine phantom, this may delay the time to accrue the first patient. After this initial 6 month period, it is projected that this study will accrue 5 patients per month and that it will take 15 months to accrue the sample size of 43 patients for the phase II component. If the average monthly accrual for the last 6 months of the phase II component is less than 3, the phase III component will not be undertaken.

If the phase III component is pursued, patient accrual would be expected to increase to at least 6 patients per month. It will take approximately 5.5 years (65 months) to accrue the projected sample size of 352 patients. The NRG Oncology Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually during the phase III component. If the average monthly accrual rate for the trial in the fifth and sixth quarters after study activation (i.e., in months 13-18) is less than 20% of the rate projected in the paragraph above (i.e., less than 1 patient per month), the study will close to further accrual. If the average monthly accrual rate is greater than 20% but less than 50% of projected (i.e., between 1-3 patients per month), the trial will be placed on probation for 6 months. If the average monthly accrual rate at the end of the probationary period is less than 50% of projected (3 patients per month), the study will close to future accrual.

13.4 Analysis Plan (09/23/16)

13.4.1 Phase II Analysis of Treatment Delivery

Ineligible patients and patients without treatment data will not be evaluated. Successful treatment delivery is defined as acceptable or minor variation as detailed in section 6.0. Toxicity burden will be evaluated to identify patients not completing treatment due to excessive toxicity.

Image-guided radiosurgery/SBRT will be deemed feasible in a cooperative group setting if 32 out of the 41 evaluable patients successfully complete treatment (Section 13.2.2). Given that feasibility has been established, the results will be provided to NCI for approval to proceed with the phase III component.

13.4.2 Phase III Evaluation of Treatment Response

Patients will be treated at an index spine lesion and up to 2 additional spine lesions. The index site is the lesion with the highest baseline (day of radiosurgery) pain score. If multiple sites have the same baseline pain score, the index site is the most cephalad lesion.

Scoring system for pain is a numerical 11-point scale (0-10). Patients are instructed that 0 indicates no pain and that 10 indicates the worst pain imaginable. In general, scores of 1-4 indicate mild pain, scores of 5-6 indicate moderate pain, and scores of 7-10 indicate severe pain. However, the clinical interpretation of the intermediate values will differ amongst the patients. Since patients have different perceptions and tolerances of pain, change in pain is most often the outcome of interest.

Pain response will be categorized as following: 1) complete response, post-treatment pain score of 0 at the index site; 2) partial response, post-treatment improvement of at least 3 points at the index site; 3) stable response, post-treatment pain score within 3 points of the initial pain score at the index site, or 4) progressive response, a post-treatment increase of at least 3 points at the index site. A complete, partial, or stable response at the index site requires no increase in narcotic pain medication and no increase in pain score at the secondary treated site(s). Although complete response is the best possible outcome, partial response is also a satisfactory outcome. Therefore, patients with complete or partial response will be considered responders. Any patient with a complete or partial response at the index site but a progressive response at the secondary sites will be considered a non-responder.

13.4.3 Phase III Analysis of Treatment Response

The primary endpoint is complete or partial pain response at 3 months after randomization. As noted above, partial pain relief is defined as an improvement of at least 3 points on the rating scale (and no increase in the pain score at any other treated lesion[s], with no increase in narcotic pain medication). Complete pain relief is defined as a score of 0 on the rating scale, with no increase in narcotic pain medication.

All eligible, randomized patients will be included in the analysis regardless of treatment compliance (intent-to-treat analysis). Although missing assessments should be minimized due to current improved data collection methods, up to 10% of patients are still expected not to be assessed. These patients will be included in the analysis and will be initially assumed to have the similar response rate as the assessed patients with the same baseline pain scores.

We hypothesize that the use of radiosurgery will increase the percentage of patients experiencing a complete or partial response at 3 months from the 51% response rate achieved from conventional radiotherapy to 70% with image-guided radiosurgery/SBRT, a relative increase of 40%.

$H_0: p_1 = p_2$ vs. $H_A: p_1 > p_2$
where p_i is the proportion of complete or partial responders in arm i.

The one-sided exact binomial test with a significance level of 0.025 will be used to test for differences in the response rate. Sensitivity analyses of this result using other ways of imputing pain responses for the non-assessed patients (such as all classified as nonresponders or responders) will be performed. Subset analyses based on the number of treated sites also will be performed. Descriptive statistics of the actual change scores will also be provided. The mean change score and standard deviations will be reported.

13.4.3.1 *Secondary Endpoints*

13.4.3.1.1 Rapidity of Pain Response

Patients will be assessed weekly during the first month after randomization and also at 3, 6, 12, and 24 months. The median time to pain response, as defined above, will be estimated using the Kaplan-Meier approach. (Kaplan 1958). The null and alternative hypotheses are:

$H_0: S_1(t) = S_2(t)$ vs. $H_A: S_1(t) > S_2(t)$
where $S_i(t)$ is the distribution of response times for patients in arm i

The stratified log-rank test will be used to test for a statistically significant difference in rapidity distributions with alpha=0.025 (Mantel 1966). In addition, the Cox proportional hazards regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference (1972). Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

13.4.3.1.2 Duration of Pain Response

Patients will be assessed weekly during the first month after randomization and also at 3, 6, 12, and 24 months. Pain response begins when a patient improves at least 3 points, and pain response ends when the pain score increases by 3 points or when narcotic pain medication increases. Patients dying without a reported pain relapse will be censored at the day of death. The median duration pain response will be estimated using the Kaplan-Meier approach (Kaplan 1958). The null and alternative hypotheses are:

$H_0: S_1(t) = S_2(t)$ vs. $H_A: S_1(t) > S_2(t)$
where $S_i(t)$ is the distribution of response duration times for patients in arm i

The stratified log-rank test will be used to test for a statistically significant difference in duration distributions with alpha=0.025 (Mantel 1966). In addition, the Cox proportional hazards regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference (1972). Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

13.4.3.1.3 Incidence of Adverse Events

Adverse events are reported according to the CTCAE Version 3.0. Differences in incidence rates at 3 months from the completion of treatment between the two treatment arms will be tested using the two-sided chi-square test at the 0.05 significance level. Univariate logistic regression will be used to model the distribution of acute adverse events. Multivariate logistic regression will be used to model the distribution of acute adverse events, adjusting for covariates, including, but not limited to treatment arm, prior use of pilocarpine, time since completion of chemotherapy and/or radiation, and age. Both

unadjusted and adjusted odds ratios and their respective 95% confidence interval will be computed (Hosmer 2000).

13.4.3.1.4 Treatment Differences in Quality of Life, Global Pain, and Health Utilities

Participation in the quality of life component is not mandatory in this study. However, if patients agree to participate in this component, adherence to the component assessment schedule will be encouraged through reminders from participating institutions. Completion of all scheduled assessment is part of the routine delinquency assessment for participating institutions. In spite of these efforts, missing data is to a certain extent expected.

Patients missing assessments due to death will be analyzed separately. If these patients are not equally distributed between the two treatment arms, we will conduct a sensitivity analysis to determine the impact of the exclusion. Imputation methods will be used to determine values for all alive patients missing assessments. Multiple imputation procedures provide a valid strategy for dealing with missing data sets, properly reflecting the uncertainty due to missing values. The possible strategies for imputation and analyses will depend on the severity of the missing data problem and missing pattern (MNAR, MAR, MCAR) [Little 2002].

Patient scores on the FACT subscale range from 0 to 108 with higher scores indicating improved quality of life. The change scores from pretreatment to 3 months will be compared between the treatment arms. A mean difference of 7 points represents a clinically meaningful change (CMC). A difference of less than 7 points between the treatment arms will not be considered meaningful, even if it has statistical significance. If the baseline scores are not distributed similarly between the treatment arms, the percent change scores will be used to adjust for these varying baseline values. A 7 point CMC corresponds to varying percentage changes, depending on the baseline values. The null and alternative hypotheses are:

$H_0: \Delta\mu_1 = \Delta\mu_2$ vs. $H_A: \Delta\mu_1 > \Delta\mu_2$

where $\Delta\mu_i$ is the mean FACT change score from baseline to 3 months for patients in arm i.

Assuming that the data are normally distributed, the two sample t-test assuming equal variances will be used to test the hypothesis at the 0.025 significance level. If normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis.

In addition to change in QOL at 3 months after treatment, the overall trends in pain [Brief Pain Inventory (BPI)], QOL (FACT-G), and health utilities [EuroQol (EQ-5D)] will be described with longitudinal data analysis. All indicators will be assessed pretreatment and at 3, 12, and 24 months post-treatment. Specifically, the general linear mixed-effect model will be used to describe the change trend of these scores over time, allowing for adjustments using covariates of interest (Verbeke 2000).

13.4.3.1.5 Treatment Response and Quality of Life

In addition to evaluating treatment differences in QOL, of particular interest is the relationship between treatment response and QOL. In RTOG 9714, sixty-six percent (167/253) of spine metastases patients completed both the baseline and the three-month FACT-G while 34% did not. The distributions of pretreatment variables for the patients with and without both FACT-G assessments were similar. Patients with pain relief showed significantly more improvement in the FACT-G total score, most of which was due to improvements seen in both the functional well-being (FWB) and the physical well-being (PWB) subscales. The difference in mean change scores between responders and nonresponders was 9.8 [95% CI (2.3, 17.3), p=0.01] for the FACT-G total score. Therefore, the change scores from pretreatment to 3 months post-treatment between patients who respond to treatment and patients who do not respond to treatment will be compared in RTOG 0631. The null and alternative hypotheses are:

$H_0: \Delta\mu_1 = \Delta\mu_2$ vs. $H_A: \Delta\mu_1 > \Delta\mu_2$

where $\Delta\mu_i$ is the mean FACT change score from baseline to 3 months for patients in response group i.

Assuming that the data are normally distributed, the two sample t-test assuming equal variances will be used to test the hypothesis at the 0.025 significance level. If normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis.

13.5 Interim Reports to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared twice a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain treatment efficacy results with respect to the primary or the secondary endpoints.

The NRG Oncology Data Safety and Monitoring Board (DSMB) will monitor the phase II component of the study for safety and feasibility. The NRG Oncology Data Monitoring Committee (DMC) will monitor the phase III component of the study for safety and efficacy.

This study also will be monitored by the Clinical Data Update System (CDUS), v. 3.0. Quarterly CDUS reports are submitted electronically.

13.6 Reporting the Initial Treatment Results

The primary hypothesis of this study is to determine the efficacy of image-guided radiosurgery/SBRT in treating painful spine metastases. This initial efficacy analysis will occur after each patient has been potentially followed for at least 3 months following completion of treatment. The long-term efficacy analysis will occur after each patient has been potentially followed for at least 24 months. The analyses will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and the secondary endpoints. The primary hypothesis of radiosurgery benefit will be tested using the exact binomial test as specified in the analysis plan (Section 13.4.2). Also, where feasible, comparisons with respect to all endpoints will be made by each gender, racial, and ethnic category.

13.7 Gender and Minorities (4/21/14)

In conformance with the national Institutes of Health *(NIH)* Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of women and minorities will be examined during the interim reports. Based on accrual statistics from RTOG 9714, the projected accrual by gender, race, and ethnicity for both phases is shown below:

Projected Distribution of Gender and Minorities

	Gender		
	Males	**Females**	**Total**
Ethnic Category			
Hispanic or Latino	5	7	12
Not Hispanic or Latino	173	210	383
Ethnic Category: Total of all subjects	**178**	**217**	**395**
Racial Category			
Native American or Alaskan Native	3	3	6
Asian	3	3	6
Black or African American	29	35	64
Native Hawaiian or other Pacific Islander	4	6	10
White	139	179	318
Racial Category: Total of all subjects	**178**	**217**	**395**

REFERENCES

Badia, X., Herdman, M., Kind, P. The influence of ill-health experience on the valuation of health. *Pharmacoeconomics*. 13: 687-696, 1998.

Bissonnette J. Quality assurance of image-guidance technologies." *Sem Radiat Oncol*. 17: 278-286, 2007.

Black P: Spinal metastases: Current status and recommended guidelines for management. *Neurosurg.* 5: 726-746, 1979.

Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomized comparison with a multifraction schedule over 12 months of patient follow-up. On behalf of the Bone Pain Trial Working Party. *Radiother Oncol.* 1999;52:111-121; 1999.

Cella DF, Tulsky DS, Gray G, Sarafian B, et al. The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *J Clin Oncol.* 11: 570-579, 1993.

Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure *J Neurosurg Spine*. 7:151-160, 2007.

Cleeland CS. Measurement of pain by subjective report. In: Chapman CR; Loeser JD, editors. *Issues in pain measurement*. New York: Raven Press; 1989: 391-403.

Daut RL, Cleeland SS, Flannery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*. 14: 197-210, 1983.

Degen JW, Gagnon GJ, Voyadzis JM, et al. CyberKnife stereotactic radiosurgical treatment of spinal tumors for pain control and quality of life. *J Neurosurg Spine.* 2: 540-5499, 2005.

Gerszten PC, Burton SA, Welch WC, Brufsky AM, Lembersky BC, Ozhasoglu C, Vogel WJ. Single-fraction radiosurgery for the treatment of spinal breast metastases. *Cancer.* 104: 2244–2254, 2005.

(b) Gerszten PC, Burton SA, Ozhasoglu C, Vogel WJ, Welch WC, Baar J, Friedland DM. Stereotactic radiosurgery for spine metastases from renal cell carcinoma. *J Neurosurg Spine.* 3(4): 288-295, 2005.

(c) Gerszten PC, Burton SA, Quinn AE, Agarwala SS, Kirkwood JM. Radiosurgery for the treatment of spinal melanoma metastases. *Stereotact Funct Neurosurg.* 83: 213-221, 2005.

Gerszten PC, Burton SA, Belani CP, et al. Radiosurgery for the treatment of spinal lung metastases. *Cancer.*107:2653–2661, 2006.

Greenberg HS, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: Results with a new treatment protocol. *Ann Neurol*. 8: 361-366, 1980.

Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastasis. *JNCI*. 97: 798-804, 2005.

Helweg-Larsen S. Clinical outcome in metastatic spinal cord compression: A prospective study of 153 patients. *Acta Neurol Scand*. 94:269-275, 1996.

Ho AK, Fu D, Cotrutz C, et al. A study of the accuracy of cyberknife spinal radiosurgery using skeletal structure tracking. *Neurosurg*. 60(Suppl 1):147-156, 2007.

Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York: John Wiley & Sons; 2000.

Jemal A, Murray T, Ward E, et al. Cancer statistics, *AC Cancer J Clin*. 55: 10-30, 2005.

Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. *Pain*. 83: 157-62, 1999.

Jin R, Rock J, Jin JY, el al. Image-guided spinal radiosurgery for epidural compression of multiple myeloma. *Intl J Rad Oncol Biol Phys*. 66:S244, 2006.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Statist Assoc*. 53: 457-481, 1958.

Little RJ, Rubin DB. *Statistical Analysis with Missing Data*. 2nd ed. New York: John Wiley; 2002.

Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother*. Rep 50: 163-170, 1966.

Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: Final results from a prospective trial. *Int J Radiat Biol Phys*. 15: 959, 1995.

Nguyen QN, Shiu AS, Rhines LD, Wang H, Allen PK, Wang XS, Chang EL. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys.* 15:1185-92, 2010.

Patchell R, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Young B. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomized trial. *Lancet*. 366: 643-648, 2005.

Potters L, Steinberg M, Rose C, et al. American Society for Therapeutic Radiology and Oncology and American College of Radiology practice guideline for the performance of stereotactic body radiation therapy. *Intl J Rad Oncol Biol Phys*. 60:1026-1032, 2004.

Rabin, R., de Charro, F. EQ-5D: A measure of health status from the EuroQol Group. *Ann Med*. 33: 337-343, 2001.

Ryu S, Yin FF, Rock J, et al. Image-guided and intensity-modulated radiosurgery for spinal metastasis. *Cancer*. 97: 2013-2018, 2003.

Ryu S, Rock J, Rosenblum M, Kim JH. Pattern of failure after single dose radiosurgery for single spinal metastasis. *J Neurosurg.* 101: 402-405, 2004.

Ryu S, Jin JJ, Jin RY, Rock J, Ajlouni M, Movsas B, Kim JH. Partial Volume Tolerance of Spinal Cord and Complication of Single Dose Radiosurgery. *Cancer*. 109:628-636, 2007.

Ryu S, Jin R, Jin JJ, Qing C, Rock J, Anderson J, Movsas B. Pain Control by Image-guided Radiosurgery for Solitary Spinal Metastasis. *J Pain Sympt Manage*. 35: 292-298, 2008.

(b) Ryu S, Gerszten PC. Treatment failure and complications. In Gerstzen PC, Ryu S. eds. *Spine Radiosurgery*. New York, NY: Thieme; 2008: 104-111.

(c) Ryu S, Rock J, Jain R, et al. *Radiosurgical Decompression of Epidural Spine Metastasis.* 2008. (In review).

Schulz, M., Chen, J., Woo, H., et al. A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol*. 168: 155-159, 2002.

Steenland ES, Leer J, van Houwelingen H, et al. The effect of a single fraction to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol*. 52:101-109, 1999.

Timmerman R. Overview of hypofractionation. Sem Rad Oncol. 2008. (In print)

Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastasis: Final results of the study by Radiation Therapy Oncology Group. *Cancer.* 50:893-899, 1982.

Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. New York: Springer-Verlag, Inc; 2000.

Wu JS, Wong JR, Johnson M, Bezjak A, Whelan T. Cancer Care Ontario Practice Guidelines Initiative Supportive Care Group. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys*. 55: 594-605, 2003.

Yamada Y, Bilsky MH, Lovelock M, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spine al lesions. *Int J Radiat Oncol Biol Phys*. 71:484-490, 2008.

Yin FF, Ryu S, Ajlouni M, et al. A technique of intensity–modulated radiosurgery (IMRS) for spinal tumors. *Med Phys*. 12: 2815-2822, 2002.

(b) Yin FF, Zhu JG, Yan H, Guan H, Hammond R, Ryu S, Kim JH. Dosimetric characteristics of Novalis shaped beam surgery unit. *Med Phys*. 29: 1729-1738, 2002.

Yin FF, Wang Z, Yoo S, et al. Integration of cone-beam CT in stereotactic body radiation therapy. *Tech in Cancer Res & Treatment (TCRT)*. 7(2):133-140, 2008.

Yoo S Kim GY, et al. A quality assurance program for the on-board imagers. *Med Phys*. 33(11): 4431-47, 2006.

Young RF, Post EM, King GA. Treatment of spinal epidural metastasis: Randomized prospective comparison of laminectomy and radiotherapy. *J Neurosurg.* 53: 741, 1980.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis*. 27: 365-375, 1974.

APPENDIX I (09/23/16)

STUDY PARAMETER TABLE:

PHASE II COMPONENT (8/30/11)

Assessments	Pre-Treatment	Day of Treatment	Follow-up: At 1 and 3 months from registration
History/physical	Within 2 wks prior to registration		X
Performance status	Baseline		X
Neurological exam	Within 1 wk prior to registration		X
MRI of the spine	Within 4 wks prior to registration		At 3 months from registration only
Numerical Pain Scale and documentation of patient's pain medication	Within 1 wk prior to registration		
Adverse event evaluation			X

See Phase III Component on next page

APPENDIX I (Continued) (09/23/16)

STUDY PARAMETER TABLE: **Also see Section 11.2 for details**

PHASE III COMPONENT

Assessments	Pre-Treatment	1 month from randomization	Follow-up: At 3, 6, 12, 24 months from randomization
History/physical	Within 2 wks prior to registration		X
Performance status	Baseline		X
Neurological exam	Within 1 wk prior to registration		X
MRI of the spine	Within 4 wks prior to registration		X
Numerical Pain Scale and documentation of patient's pain medication*	Within 1 wk prior to registration	(On the day of treatment) (At home: At 1, 2, and 3 weeks; bring to clinic at 1 month) In clinic at 1 month	X
FACT-G (FA), BPI (QL), EQ-5D (HP)	Baseline		At 3, 6, 12 and 24 months from randomization
Adverse event evaluation		X	X
Blood & urine for banking and translational research	Recommended		Recommended at 3 months from randomization

*NRPS at 3 months is required for analysis of the primary endpoint

APPENDIX II (09/23/16)

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed or**
5	**Death**

APPENDIX III (09/23/16)

RTOG 0631 Neurological Examination

1. Tenderness over the spine (Mark the spine level of tenderness on percussion)

☐ C1 ☐ C2 ☐ C3 ☐ C4 ☐ C5 ☐ C6 ☐ C7 ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐ T5 ☐ T6 ☐ T7 ☐ T8 ☐ T9 ☐ T10 ☐ T11 ☐ T12

☐ L1 ☐ L2 ☐ L3 ☐ L4 ☐ L5 ☐ sacrum

2. Radiculopathy (If present, mark all levels)

☐ C1 ☐ C2 ☐ C3 ☐ C4 ☐ C5 ☐ C6 ☐ C7 ☐ C8 ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐ T5 ☐ T6 ☐ T7 ☐ T8 ☐ T9 ☐ T10 ☐ T11 ☐ T12

☐ L1 ☐ L2 ☐ L3 ☐ L4 ☐ L5 ☐ S1

3. Muscle strength of the extremities: (Mark 0-5 strength for each)

Arm Muscles		Strength		Leg muscles		Strength	
		Right	Left			Right	Left
Deltoid	C5/6			Iliopsoas	L2/3/4		
Biceps	C5/6			Quadriceps	L2/3/4		
Triceps	C6/7/8			Hamstrings	L4/5/S1		
Digit Flex (hand grip)	C7/8/T1			Ant Tibialis	L4/5		
Interossei	C8/T1			Gastrocnemius Soleus	L5/S1/2		

Modified MRC grade of muscle strength

5 Normal strength

5- Equivocal, barely detectable weakness

4+ Definite, but slight weakness

4 Able to move against gravity with resistance

3 Able to move against gravity without resistance

2 Active movement without gravity

1 Flicker or trace of movement.

0 No palpable muscle contraction

Continued on next page

4. Sensory change; Pinprick (Mark normal or decreased)

	Arm		Trunk		Leg	
	Right	**Left**	**Right**	**Left**	**Right**	**Left**
Normal						
Decreased						

5. Urinary incontinence (in patients who had initial abnormality or developed new symptom)

Yes_____ or No_____

6. Anal sphincter tone (in patients who had initial abnormality or developed new symptom)

Normal_____ Decreased_____ or None_____

APPENDIX IV (09/23/16)

NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood *(as specified by the protocol)*:

Kit contents: Note: Sites are expected to supply their own blood draw tubes.

- Twenty-five (25) 1 ml cryovials for all timepoints
- Biohazard bags (5) and Absorbent shipping material (5)
- One (1) Styrofoam container (inner) and Cardboard shipping (outer) box per case
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (STF) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube (one 10 ml or two 5 ml)

- ❑ Label five (5) 1ml cryovials as necessary for the serum collected. Label them with the NRG study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the Specimen Transmittal (ST) Form.
3. Aliquot a minimum of 0.5 ml serum into five (5) for the serum collected with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the Specimen Transmittal (ST) Form.

(B) Plasma (If requested): Purple Top EDTA tube #1 (one 10 ml or two 5 ml)

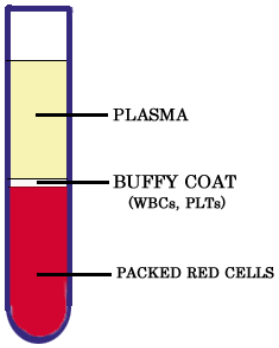
- ❑ Label five (5) 1ml cryovials as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the Specimen Transmittal (ST) Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma into five (5) cryovials for the plasma collected labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the Specimen Transmittal (ST) Form.

(continued on next page)



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2 (one 5 ml or one 10 ml)

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze tubes upright immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

(continued on next page)

NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu

APPENDIX V (09/23/16)
NRG ONCOLOGY URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents: For two timepoints

- Two (2) Sterile Urine collection cup
- Two (2) 7 ml disposable pipettes
- Absorbent paper towel
- Four (4) 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the NRG Oncology study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with NRG Oncology study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- ❑ Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
  - Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)

NRG Oncology Biospecimen Bank-San Francisco at University of California San Francisco
2340 Sutter Street, Room S341, San Francisco, CA 94115
Contact Phone: (415) 476-7864