

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0631

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

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0631

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

SCHEMA

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	N	Single fraction dose of 16 Gy
A	2) 2-3	D	
T		O	Arm 2: External Beam Radiation Therapy:
I		M	Single fraction dose of 8 Gy
F		I	
Y		Z	Randomization ratio (Arm 1: Arm 2) = 2:1
		E	

See Section 5.0 for pre-registration requirements; see Section 6.0 for details of radiosurgery; see Section 11.2 and Appendix II 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
Phase III component: 240 patients

- ____ (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 (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 ≥ 3 mm 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, lymphoma, renal cell carcinoma, or melanoma?
- ____ (N) 14. Is the patient non-ambulatory?
- ____ (N) 15. Is there spinal instability due a compression fracture?
- ____ (N) 16. Is $> 50\%$ of the vertebral body height present?
- ____ (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. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the patient provided study-specific consent prior to study entry
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Method of Payment
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date
- _____ 17. Registration/randomization date: This date will be populated automatically.

(Continued on next page)

RTOG Institution #
RTOG 0631
Case #

ELIGIBILITY CHECKLIST (8/7/09)
(page 3 of 3)

- _____(Y/N) 18. Blood kept for cancer research?
_____(Y/N) 19. Urine kept for cancer research?
_____(Y/N) 20. Blood kept for medical research?
_____(Y/N) 21. Urine kept for medical research?
_____(Y/N) 22. Allow contact for future research?

For Phase III Component Only:

_____(N/Y) 21. Did the patient agree to participate in the quality of life component?

- _____ If no, please specify the reason from the following:
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 _____

_____ 22. Specify number of spine metastases (1 vs. 2-3)

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/RTOG 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

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).

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, this study will use 16 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].

1.4 Advantages of Image-Guided Radiosurgery

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 RTOG 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). The result will indeed demonstrate whether or not there is radiation dose-response in pain control of bone metastasis.

1.5 Hypothesis

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 RTOG cooperative group 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 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.

1.6 Primary Endpoint: Numerical Rating Pain Scale (NRPS)

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.**

1.6.3 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

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/translation/translation_landing.aspx.

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

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 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) (11/6/09)

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 CTEP Active Version of the CTCAE;

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

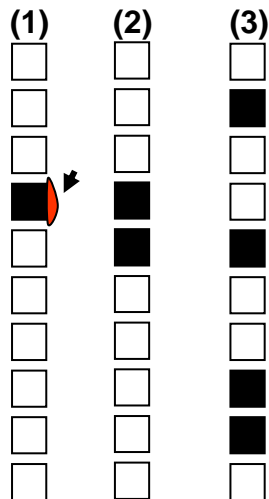
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

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.

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



3.1.2 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 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. 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 IV 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

- 3.2.1 Histologies of myeloma, lymphoma, renal cell carcinoma, or melanoma;
- 3.2.2 Patients with any spine metastasis with a rating of 5 on the Numerical Rating Pain Scale that is not planned to be treated with radiosurgery;
- 3.2.3 Non-ambulatory patients;
- 3.2.4 Spine instability due to a compression fracture;
- 3.2.5 > 50% loss of vertebral body height;
- 3.2.6 Frank spinal cord compression or displacement or epidural compression within 3 mm of the spinal cord;
- 3.2.7 Patients with rapid neurologic decline;
- 3.2.8 Bony retropulsion causing neurologic abnormality;
- 3.2.9 Prior radiation to the index spine;
- 3.2.10 Patients for whom an MRI of the spine is medically contraindicated;
- 3.2.11 Patients allergic to contrast dye used in MRIs or CT scans.

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)

- 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.

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. 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

Note: Participating institutions must irradiate a special spine phantom in order to enter patients on this study. This phantom is designed to credential sites for the IMRT component of the study. An additional step is the credentialing that sites must do for IGRT. Sites previously credentialed for IMRT and IGRT will not be automatically credentialed for this study. See details below in Sections 5.1 and 5.2.

5.1 Pre-Registration Requirements for Spine Radiosurgery/SBRT

- 5.1.1 The institution must complete all relevant parts of the RTOG 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. In addition, an SFTP account for digital data submission must be established, as data will be submitted digitally to the Image-Guided Therapy Center (ITC) [see Section 12.2]. Information for completing both of these tasks is available on the Advanced Technology (ATC) web site at <http://atc.wustl.edu>. The ATC is comprised of RTOG RT Quality Assurance, the Image-Guided Therapy Center (ITC) at Washington University, and the Radiological Physics Center (RPC) at MD Anderson Cancer Center.

5.1.2 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 the RPC**. Instructions for requesting and irradiating the spine phantom are available on the RPC web site at <http://rpc.mdanderson.org/rpc/>; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement.

5.2 **Additional Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT)**

5.2.1 IGRT Credentialing Process

5.2.1.1 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 treatment images along with a spreadsheet of IGRT data to ATC from an anonymized patient treated similarly to 0631 but **not** accrued to the study.
- The Medical Physics Co-Chair, Dr. Yin, will review the images and spreadsheet and upon his approval of them, RTOG Headquarters will notify the institution to enroll a patient on 0631 and to submit a series of treatment images along with a spreadsheet of IGRT data for that patient to the ATC.
- Dr. Yin will review the images and spreadsheet, and upon his approval of this data for the patient enrolled on 0631, RTOG Headquarters will notify the institution that this part of the credentialing is complete and the institution can continue to enroll patients on 0631.

See the ATC web site, <http://atc.wustl.edu>, to obtain the spreadsheet. Since this study involves a single fraction treatment of the spine, images of the simulation position, reposition, and pretreatment, and an image 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.

5.2.1.2 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.

For the 3D and 2D imaging techniques, acceptable and unacceptable discrepancies for the post-treatment imaging are defined as follows:

< 2 mm	Per protocol
2 mm but 3 mm	Variation acceptable
> 3 mm	Deviation unacceptable (patient will not be accrued to the study)

5.3 Regulatory Pre-Registration Requirements

5.3.1 **U.S. sites and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution's first case:

- § IRB/REB approval letter;
- § IRB/REB approved consent (English Version)
- § IRB/REB assurance number

5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

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

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 format to the ITC, <http://atc.wustl.edu>. This must include both the IGRT images and the treatment planning images.

6.3 Treatment Planning/Target Volumes

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.

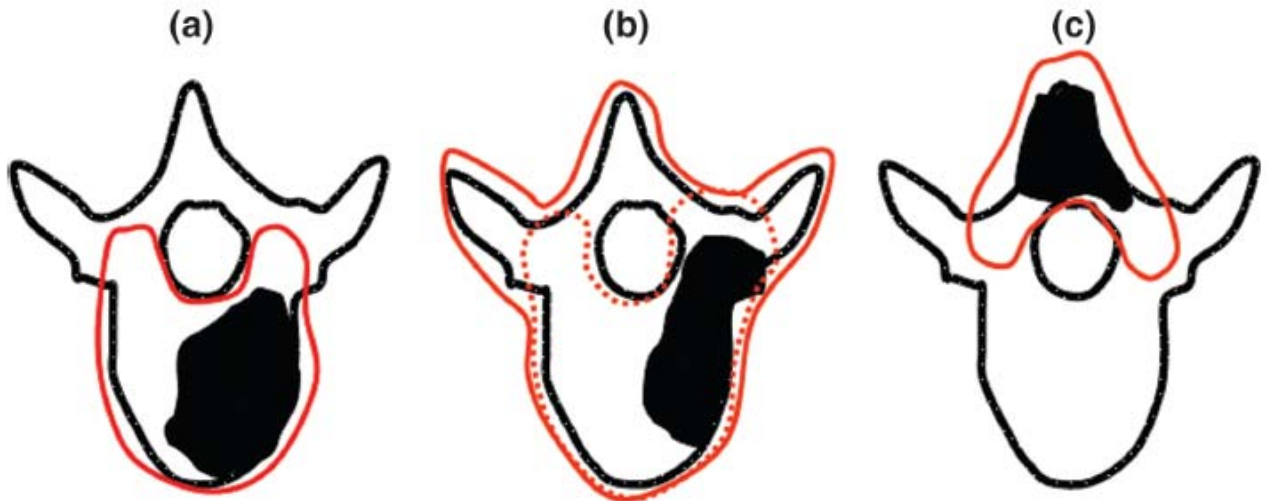


Figure 2: Diagram of Spine Metastasis and Target Volume

6.3.1.2 Spinal Cord Volume

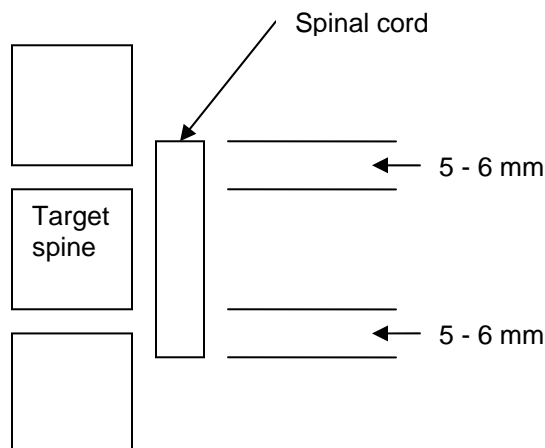
Two spinal cord contour sets are required for this protocol: the conventional and the partial spinal cord volumes.

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 RTOG protocols.

The partial spinal cord volume is specific to this study. The definition of partial spinal cord volume is shown in Figure 3 below. 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 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.

The partial spinal cord dose constraint is 10 Gy to no more than 10% of the spinal cord volume defined as from 5-6 mm above to 5-6 mm below the target volume [Ryu 2008]. The absolute spinal cord dose is 10 Gy to the spinal cord volume to less than 0.35 cc. The partial or absolute volume spinal cord constraints are applied to each treated spine level when the patient has multiple spine levels treated. Any spinal cord dose exceeding this constraint 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 constraint. 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 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 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 minor violation, and any coverage of < 80% of the target volume is a major deviation.

2) Target Dose Heterogeneity

The treatment plan is acceptable 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

a) Location

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. Any dose greater than 105% of the prescription dose should not occur 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.

b) Volume

The most important requirement is the spinal cord dose constraint 10Gy to the 10% of the partial spinal cord volume defined as 5-6 mm above and below the target. The absolute spinal cord dose is 10 Gy to the spinal cord volume less than 0.35 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

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).

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

Serial Tissue	Volume	Volume Max (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	<0.035 cc <0.35cc <1.2 cc (SBRT only)	14 Gy 10 Gy 7 Gy (SBRT only)	myelitis
<i>Cauda Equina</i>	<0.035 cc <5 cc	16 Gy 14 Gy	neuritis
Sacral Plexus	<0.035 cc <5 cc	18 Gy 14.4 Gy	neuropathy
Esophagus*	<0.035 cc <5 cc	16 Gy 11.9 Gy	stenosis/fistula
Ipsilateral Brachial Plexus	<0.035 cc <3 cc	17.5 Gy 14 Gy	neuropathy
Heart/Pericardium	<0.035 cc <15 cc	22 Gy 16 Gy	pericarditis
Great vessels*	<0.035 cc <10 cc	37 Gy 31 Gy	aneurysm
Trachea* and Larynx	<0.035 cc <4 cc	20.2 Gy 10.5 Gy	stenosis/fistula
Skin	<0.035 cc <10 cc	26 Gy 23 Gy	ulceration
Stomach	<0.035 cc <10 cc	16 Gy 11.2 Gy	ulceration/fistula
Duodenum*	<0.035 cc <5 cc	16 Gy 11.2 Gy	ulceration
Jejunum/Ileum*	<0.035 cc <5 cc	15.4 Gy 11.9 Gy	enteritis/obstruction
Colon*	<0.035 cc <20 cc	18.4 Gy 14.3 Gy	colitis/fistula

Rectum*	<0.035 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 absolute spinal cord dose is 10 Gy to the spinal cord volume less than 0.35 cc. This was calculated based on the published data of the spinal cord dose constraint 10 Gy to 10% of the spinal cord volume drawn as 5-6 mm above and below the target volume (Ryu 2008).

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

6.4.2 Contouring of Normal Tissue Structures

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

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.

6.6 Compliance Criteria

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 minor violation, and coverage of < 80% is a major deviation. 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.

6.6.2 Treatment Delivery Compliance

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 (8/11/09)

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 the Image-Guided Therapy Center (ITC), Washington University, St. Louis, MO 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, either remotely or at RTOG semi-annual meetings. 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 RTOG Headquarters, 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.

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
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 Arm 2, external beam radiotherapy, the prescribed dose is 8 Gy in 1 fraction. Treatment volume will include the involved index spine, plus one spine level superior and one spine level inferior to the index spine.

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 radiosurgery.

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. 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 simulator and portal film with digital format documenting that the treatment site is adequately covered and verified by the treating Radiation Oncologist.

6.8.3 Treatment Planning/Target Volumes

Treatment target volume will include the involved index spine, plus one spine level superior and one spine level inferior to the index spine.

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. As stated above, IMRT is not allowed for Arm 2.

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.

6.8.4 Critical Structures

Since this treatment is conventional radiotherapy, 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.

6.8.5 Documentation Requirements

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

All criteria for credentialing listed in Section 5.1 must be completed. No institution will be allowed to enroll patients without credentialing for spine radiosurgery and IGRT.

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 immunocompromised 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 (11/6/09)

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 Adverse Event Expedited Reporting System (AdEERS) application as directed in this section.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

[CTEP, *NCI Guidelines: Adverse Event Reporting Requirements*. January 2005; <http://ctep.cancer.gov/reporting/adeers.html>]

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. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

AdEERS REPORTING REQUIREMENTS

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading all adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following tables using the AdEERS application. AdEERS can be accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)). Use the patient’s case number without any leading zeros as the patient ID when reporting via AdEERS. In order to ensure consistent data capture, AEs and SAEs reported using AdEERS must also be reported to RTOG on the AE case report form (see Section 12.1). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- § **Phase II & III Studies: All unexpected potentially related SAEs**
- § **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpected	Expected
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization		
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpected	Expected
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	Not Required	Not required	Not required
Possible Probable Definite	10 Calendar Days	Not required	Not required	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

- Expedited AE reporting timelines defined:
 - Ø “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
 - Ø “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following protocol treatment or procedure.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

RTOG REPORTING REQUIREMENTS

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading all adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via AdEERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

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

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at <http://ctep.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

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

For patients who have consented to participate in the specimen submission component of the study (See Appendix I).

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

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. The RTOG encourages participants in protocol studies to consent to the banking of their specimens. The RTOG Tissue 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 RTOG Biospecimen Resource will provide collection kits and instructions at no charge for the submission of specimens in this protocol; see Appendices V and VI.

In this study, it is strongly encouraged that blood (serum/plasma/lymphocytes) and urine be submitted to the RTOG Biospecimen Resource for the purpose of banking and for translational research. If the patient consents, blood and urine will be collected at baseline and 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 buffy coat 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 Serum, Plasma, and Lymphocyte Collection for Translational Research (11/6/09)

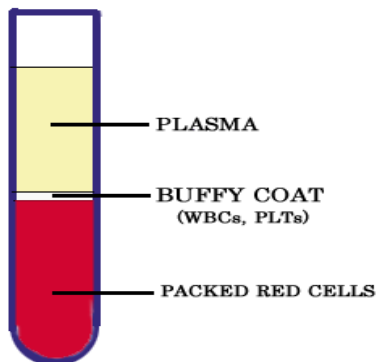
See Appendix V for blood collection kit and detailed collection instructions.

10.2.1 Blood Sample Preparation

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

10.2.2 Buffy Coat Cell and Plasma:

For a visual explanation of Buffy coat, please refer to diagram below.



10.2.3 Frozen Plasma Samples for Biomarker Analysis

- Collect one 10 ml tube of blood using one EDTA (purple top) tube.
- Invert six to seven times to ensure adequate mixing with anticoagulant.
- Centrifuge within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
- If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- Carefully pipette and transfer ~1ml aliquots of plasma into 4-5 cryovials taking care to avoid collecting any blood cells (red/white blood cells).
- Place tops on cryovials and make sure tops of cryovials are on securely.
- Tube should be clearly labeled (see Section 10.5).
- Place tubes in a Styrofoam holder and then place into a zip lock bag.
- See Section 10.5 for storage conditions.

10.2.4 Blood Sample for Isolation of Lymphocytes

- Collect one 10 ml tubes of blood using one EDTA (purple top) tube. You may use the same tube that the plasma was collected from.
- Carefully remove plasma close to the buffy coat.
- Remove the buffy coat cells carefully and place into three (3) 1ml cryovials labeled "buffy coat" (it is okay if a few packed red cells are inadvertently collected in the process).
- Tubes should be clearly labeled (see Section 10.5).
- Place all three cryovials in a Styrofoam holder and then place into a zip lock bag.
- See Section 10.5 for storage conditions.

10.2.5 Frozen Serum Samples for Biomarker Analysis

- Collect one 10 ml tube of blood without coagulants (Red top).
- Sit at room temperature for 30 min to allow clot formation.
- Centrifuge in a standard clinical centrifuge at 3000g at 4o Celsius for 30 minutes.
- Transfer ~1ml aliquots of separated serum into 4-5 cryovials.
- Place tops on cryovials and make sure tops of cryovials are on securely.
- Tube should be clearly labeled (see Section 10.5).
- Place tubes in a Styrofoam holder and then place into a zip lock bag.
- See Section 10.5 for storage conditions.

10.3 Urine Collection for Translational Research (11/6/09)

See Appendix VI for detailed collection instructions.

10.3.1 Urine Sample Collection

- a. 10 ml urine will also be collected in the morning of each day when blood is collected for potential biomarker-related study
- b. Tube should be clearly labeled (see Section 10.5).
- c. Place tubes in a Styrofoam holder and then place into a zip lock bag.
- d. See Section 10.5 for storage conditions.

10.4 Documentation for Submission of Serum, Plasma, Lymphocytes, and Urine

The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, lymphocytes, and urine; the RTOG protocol number; the patient's case number; and method of storage (e.g., stored at -80° C), must be included.

10.4.1 Specimen Collection Summary

Specimens taken from patient:	Submitted as:	Shipped:
5-10 mL of whole blood in red-top tube and centrifuge for serum	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials	Serum sent frozen on dry ice via overnight carrier
5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for plasma	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials	Plasma sent frozen on dry ice via overnight carrier
5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat	Frozen buffy coat samples in 1 mL cryovials	Buffy coat sent frozen on dry ice via overnight carrier
10-25 mL clean-catch urine	Frozen urine samples containing a minimum of 5 mL unpreserved urine in a sterile collection container	Urine sent frozen on dry ice via overnight carrier

10.5 Storage Conditions (11/6/09)

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 Form the storage conditions used and time stored.

10.6 Submit materials for Banking and Translational Research as follows:

Mailing Address: For Non-frozen Specimens Only

**RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800**

Courier Address (FedEx, UPS, etc.): For Frozen Specimens

**RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115**

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.6 Reimbursement

RTOG will reimburse submitting institutions \$50 per case for urine and \$300 per case for complex material (blood, serum, buffy coat cells). After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.7 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/biospecimen/tissuefaq.html> for further details.)

10.7.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource 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

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

11.2 Evaluations: Phase III Component

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. 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, 6, 12, and 24 month clinic visits.

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/translation/licensure.aspx>.

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 <http://www.mdanderson.org/departments/prg/>; click on "symptom assessment tools". If a translation is used, the site must transcribe the data to the appropriate RTOG 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**

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 RTOG Headquarters Data Management for instructions. If the patient is registered but does not receive image-guided radiosurgery protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 **DATA COLLECTION**

Data should be submitted to:

RTOG Headquarters*
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**

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] † The Brief Pain Inventory (BPI) (QL) † The EuroQol (EQ-5D) [HP] †	Within 2 weeks of study entry
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, 6, 12, and 24 months post-study entry
The Functional Assessment of Cancer Therapy-General (FACT-G) [FA] † The Brief Pain Inventory (BPI) (QL) † The EuroQol (EQ-5D) [HP] †	At 3, 6, 12, and 24 months post-study entry

† For Phase III component only

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) (11/6/09)

Item	Due
Preliminary Dosimetry Information (DD)	
†Digital Data Submission – <u>Treatment Plan</u> submitted to ITC via SFTP account exported from treatment planning machine by Physicist	Within 1 week post-radiosurgery
Digital data submission includes the following:	
<ul style="list-style-type: none"> CT data, critical normal structures, all tumor volumes and normal tissue contours (C1, C3) Digital beam geometry Doses for sets of treated beams Digital DVH data for all required critical normal structures, target volumes for total dose plan (DV) 	
Digital Data Submission Information Form (DDSI) – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/DDSI/ddsi.html)	
Hard copy isodose distributions for total dose plan as described in QA guidelines† (T6)	
NOTE: Sites must notify ITC via e-mail (itc@wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.	
Final Dosimetry Information	
Radiotherapy Form (T1) [copy to HQ and ITC]	Within 1 week post-radiosurgery

Treatment Record (T5) [copy to HQ and ITC]	
Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	
IGRT Submission	
IGRT images obtained on the day of treatment (IG)	Within 1 week post-radiosurgery
†IGRT Data Collection Spreadsheet on Set-up Variances [SG]	

†Available on the ATC web site, <http://atc.wustl.edu/>

12.2.1 Digital Data Submission to ITC

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (11/6/09)

13.1.1 Primary Endpoint

13.1.1.1 Phase II Component

Successful delivery of image-guided radiosurgery/SBRT in the RTOG cooperative group 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 CTEP Active Version of the CTCAE;

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

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 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 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 RTOG 97-14 (Section 13.2.2.1). In the subgroup of patients treated for spine metastases in 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, **the total sample size required for the phase III component would be 240 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). 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 RPC. 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 4 years (46 months) to accrue the projected sample size of 240 patients. The RTOG 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 (11/6/09)

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%.

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

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, 9, 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:

$$H_0: S_1(t) = S_2(t) \quad \text{vs.} \quad H_A: S_1(t) > S_2(t)$$

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, 9, 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:

$$H_0: S_1(t) = S_2(t) \quad \text{vs.} \quad H_A: S_1(t) > S_2(t)$$

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 CTEP Active Version of the CTCAE. 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:

$$H_0: \mu_1 = \mu_2 \quad \text{vs.} \quad H_A: \mu_1 > \mu_2$$

where μ_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:

$$H_0: \mu_1 = \mu_2 \quad \text{vs.} \quad H_A: \mu_1 > \mu_2$$

where μ_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 RTOG Data Safety and Monitoring Board (DSMB) will monitor the phase II component of the study for safety and feasibility. The RTOG 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

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 is shown below:

Projected Distribution of Gender and Minorities

	Gender		
	Males	Females	Total
Ethnic Category			
Hispanic or Latino	4	5	9
Not Hispanic or Latino	123	151	274
Ethnic Category: Total of all subjects	127	156	283
Racial Category			
Native American or Alaskan Native	2	2	4
Asian	2	2	4
Black or African American	21	25	46
Native Hawaiian or other Pacific Islander	3	4	7
White	99	123	222
Racial Category: Total of all subjects	127	156	283

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APPENDIX I

RTOG 0631

Informed Consent Template for Cancer Treatment Trials (English Language)

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

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have cancer that has spread to your spine and is causing pain.

Why is this study being done?

Multiple radiation treatments are frequently used to treat pain caused by cancer that has spread to the spine. Image-guided radiosurgery/stereotactic body radiation therapy (SBRT) is a treatment that uses highly focused x-rays to deliver a single high dose on a specific area of the body. Image-guided radiosurgery/SBRT uses special equipment to position the patient and guide the focused beams toward the area to be treated and away from normal tissue.

There are 2 parts to this study. **The part of the study you participate in depends on when you join the study. You will participate in Part A OR Part B but not both.**

Part A: The purpose of this part of the study is to treat the cancer that has spread to your spine and is causing pain with image-guided radiosurgery/SBRT.

Part B: The purpose of this part of the study is to compare the effects, good and/or bad, of image-guided radiosurgery/SBRT to standard radiation therapy to find out which treatment provides the most rapid pain relief with the least side effects.

How many people will take part in the study?

About 43 people will participate in Part A. About 240 people will participate in Part B.

What will happen if I take part in this research study? (11/6/09)

Part A: Before receiving a radiosurgery/SBRT treatment, you will have a treatment planning session. You will lie in a specific position, possibly within a frame device, while doctors check the location of the cancer that has spread to your spine and plan your treatment. A computer-assisted treatment will be designed and a radiation dose will be worked out for you. The session will last about 60-90 minutes.

Within a few days following your treatment planning session, you will receive one high dose radiation treatment to your spine. Your treatment may be given on the same day as the planning session or on the following day. This treatment will last about 60 minutes.

Your doctor may give you pain medication before the planning session and/or the radiation treatment to decrease any discomfort you may have due to the time spent in each session. Your doctor also may give you medicine to decrease any anxiety you may feel.

Part B: You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have a 67% chance of being placed in group 1 and a 33% chance of being placed in group 2.

If you are in group 1, you will receive radiosurgery/SBRT. Before receiving a treatment, you will have a treatment planning session. You will lie in a specific position, possibly within a frame device, while doctors check the location of the cancer that has spread to your spine and plan your treatment. A computer-assisted treatment will be designed and a radiation dose will be worked out for you. The session will last about 60-90 minutes. Within a few days following your treatment planning session, you will receive one high dose radiation treatment to your spine. Your treatment may be given on the same day as the planning session or on the following day. This treatment will last about 60 minutes. Your doctor may give you pain medication before the planning session and/or the radiation treatment to decrease any discomfort you may have due to the time spent in each session. Your doctor also may give you medicine or to decrease any anxiety you may feel.

If you are in group 2, you will receive standard radiation. You will lie in a specific position, and it will take about 30 minutes to set up your treatment. You will receive one standard dose radiation treatment to your spine. The treatment will last about 5 minutes. Your doctor may give you pain medication before the planning session and/or the radiation treatment to decrease any discomfort you may have due to the time spent in each session. Your doctor also may give you medicine or to decrease any anxiety you may feel.

Before you begin the study (For patients in both Part A and Part B) (11/6/09)

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical examination, including a neurologic examination (an examination to test the brain and nervous system)
- Evaluation of your ability to carry out your daily activities
- An MRI (Magnetic Resonance Imaging) of your spine (MRI: Imaging using a strong magnetic field to look at one part of your body)
- You will be asked to identify how much pain you are having by choosing a number from 0 (no pain) to 10 (the worst pain imaginable).
- You will be asked what pain medicine, if any, you are taking and what dose and how often you take the medicine.

During the study (For patients in Part B only)

You will need these tests and procedures that are being done to see how the study is affecting your body.

- You will be asked to identify how much pain you are having by choosing a number from 0 (no pain) to 10 (the worst pain imaginable). Rating your pain on this scale will take you about 1 minute each time. You will rate your pain on the day of treatment and then at home at 1, 2, and 3 weeks after you start treatment. Your study doctor will give you a form to fill out at home and you will bring it with you when you see your doctor at 1 month after you start treatment, and you will be asked to rate your pain during those visits.
- On the day of treatment, you will be asked what pain medication, if any you are taking and what dose and how often you take the medicine.
- At home you will record what pain medicine, if any, you are taking, and what dose and how often you take the medicine at 1, 2, and 3 weeks after you start treatment. Your study doctor will give you a form to fill out at home and you will bring it with you when you see your doctor at 1 month after you start treatment. Your doctor will record your pain medicine during those visits.
- At home at 1, 2, and 3 weeks after you start treatment, you will record any unusual symptoms you may be experiencing. You also will be asked about any unusual symptoms you may be experiencing when you see your doctor at 1 month after you start treatment.

In follow-up visits (For patients in both Part A and Part B)

You will need the following tests and procedures. They are being done to see how you and your cancer was affected by the treatment you received. These tests and procedures are part of regular cancer care.

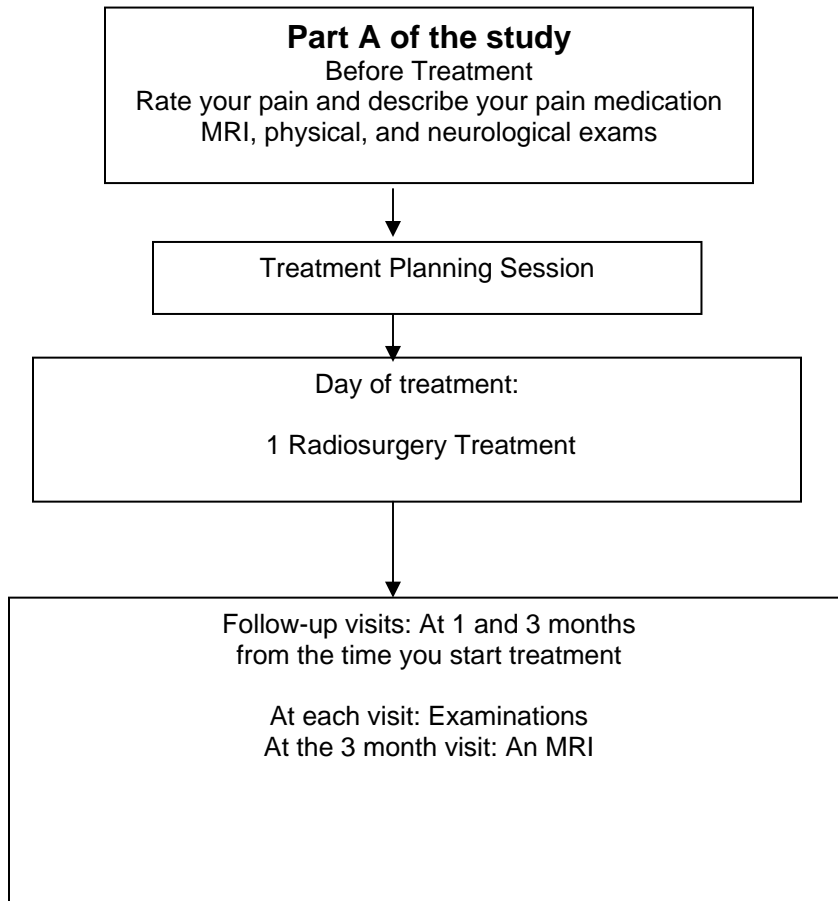
- Physical and neurological examinations
- Evaluation of your ability to carry out your daily activities
- Evaluation of any side effects you may be experiencing
- An MRI of the treated spine
- You also will be asked about any unusual symptoms you may be experiencing

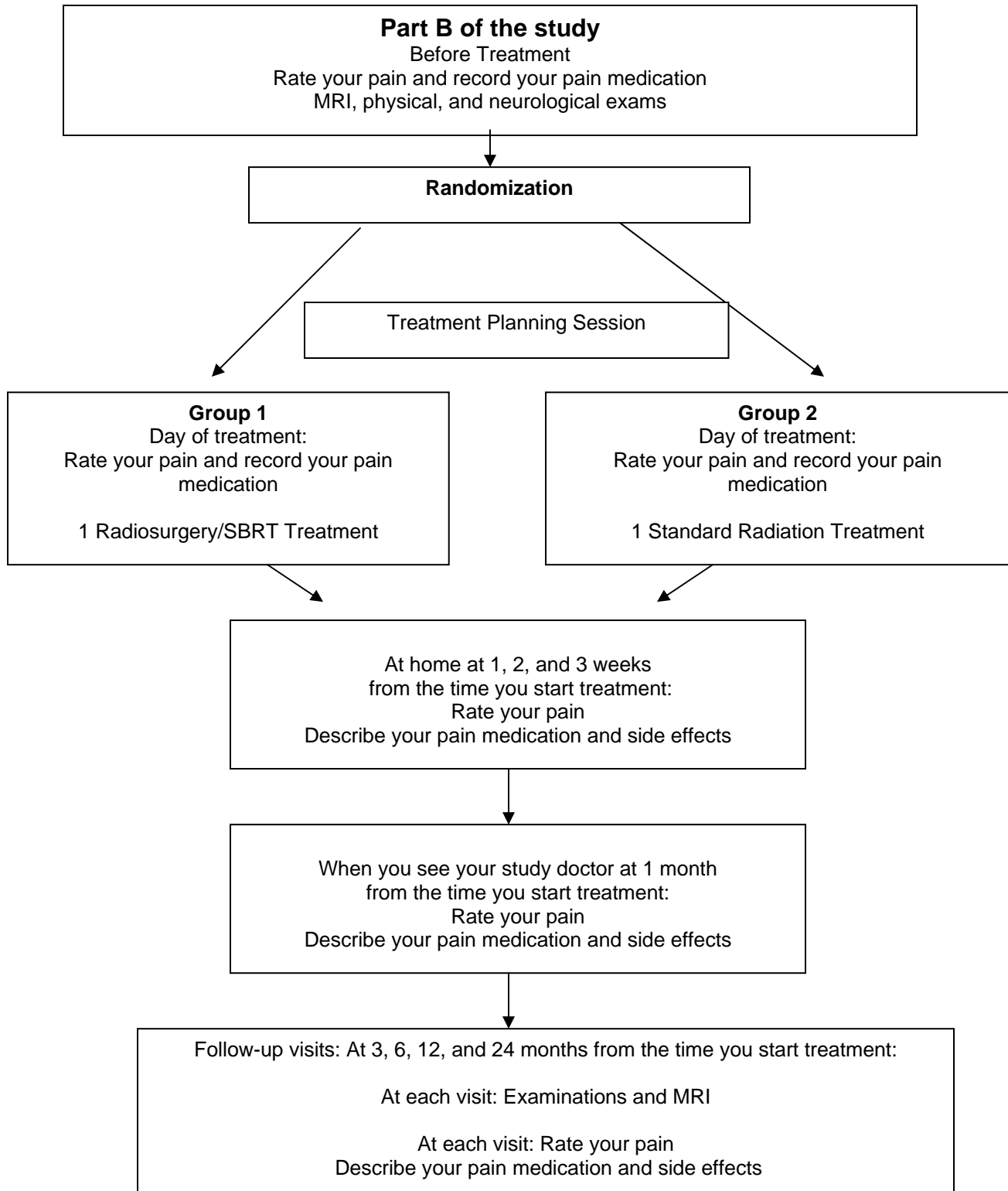
(For patients in Part B only)

- You will be asked to identifying how much pain you are having by choosing a number from 0 (no pain) to 10 (the worst pain imaginable).
- You will be asked what pain medicine, if any, you are taking and what dose and how often you take the medicine.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.





How long will I be in the study?

The part of the study you participate in depends on when you join the study. You will participate in Part A OR Part B but not both.

Patients participating in Part A: You will receive 1 radiosurgery treatment. The study doctor will see you in follow-up exams at 1 and 3 months from the time you started treatment.

Patients participating in Part B: You will receive either 1 radiosurgery treatment (group 1) or 1 standard radiation treatment (group 2). You will be seen at 1 month from the time you started treatment. Then the study doctor will see you in follow-up exams at 3, 6, 12, and 24 months from the time you started treatment.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation treatment can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the radiation treatment. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to Radiosurgery/SBRT include those which are:

Likely

The following risks are likely if you have treatment to the bones of the spine in the neck:

- Inflammation of the lining of the mouth and esophagus (passageway from mouth to stomach), which can result in difficulty swallowing, and if you cannot swallow water, dehydration can occur (your body does not have as much water and fluids as it should)
- Inflammation of the back of the throat, which can result in difficulty swallowing, and if you cannot swallow water, dehydration can occur
- Inflammation of the part of the airway that includes the vocal cords, which can result in hoarseness or loss of voice

Less Likely

- Inflammation of the lungs due to radiation treatment, which can result in cough, phlegm (thick mucous), difficulty breathing, and/or pneumonia
- Fracture or compression of the treated bones of the spine, which can result in pain and which may need nonsurgical or surgical treatment
- Discomfort or anxiety due to 60-90 minutes lying in a specific position, possibly within a frame device, for the planning session and 60 minutes for treatment; your doctor may give you medicine to decrease the discomfort and/or anxiety.

Rare but serious

- Esophageal fistula (abnormal opening in the passageway from mouth to stomach)
- Scarring of the small or large bowel, which can result in a blockage in the bowel that would require treatment
- Temporary or permanent damage to the spinal cord, which can result in:
 - Ø Skin sensations, such as burning, prickling, itching, or tingling

- Ø Muscle weakness causing inability to walk (paralysis)
- Ø Decreased ability or loss of ability to move a body part or to hold urine or control a bowel movement

Risks and side effects related to Standard Radiation include those which are:

Likely

- Hair loss in the treated area
- Skin in treatment area may become reddened, irritated, and/or dry

The following risks are likely if you have treatment to the bones of the spine in the neck:

- Inflammation of the lining of the mouth and esophagus (passageway from mouth to stomach), which can result in difficulty swallowing, and if you cannot swallow water, dehydration can occur (your body does not have as much water and fluids as it should)
- Inflammation of the back of the throat, which can result in difficulty swallowing, and if you cannot swallow water, dehydration can occur
- Inflammation of the part of the airway that includes the vocal cords, which can result in hoarseness or loss of voice

Less Likely

- Tiredness
- Low blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- If you have treatment to the abdominal area, it may result in nausea and/or vomiting, loose bowel movements, or increased frequency of urination

Reproductive risks: You should not become pregnant or father a baby while on this study because the treatment in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope that radiosurgery/SBRT rapidly relieves your pain with fewer side effects than standard radiation therapy, there is no proof of this yet. We do know that the information from this study will help researchers learn more about the effects of radiosurgery. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting radiation treatments without being in a study
- Taking part in another study
- Getting no treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at the Radiation Therapy Oncology Group (RTOG) Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

For Part A of the study: A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

For Part B of the study: A Data Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.*]

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to the following study. Below, please mark your choice.

Quality of Life Study (For patients in Part B only)

We want to know your view of how your life has been affected by cancer and its treatment. This “quality of life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at your pain, how pain affects how you feel, and how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the treatments are having. In the future, this information may help patients and doctors as they decide which treatment to use to treat cancer.

You will be asked to complete 3 questionnaires at the following times: one before treatment, then at 3, 6, 12, and 24 months from the time you start treatment.

The Questionnaires:

- The Functional Assessment of Cancer Therapy: (FACT-G) studies how you are feeling physically and emotionally during your cancer treatment and how you are able to carry out your day-to-day activities.
- The Brief Pain Inventory (BPI) looks at your pain and how pain affects how you feel.
- The EuroQol (EQ-5D) studies both the benefits and the costs of the treatments you will be given on this study. (Note: The researchers will not need patients’ social security numbers for this type of cost study).

It takes about 5 to 10 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the three questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the three Quality of Life Questionnaires.

YES

NO

About Using Blood and Urine for Research (For patients in Part B only)

We would like to collect some of your blood and urine for future research. Blood and urine for research will be collected twice, at the same time you are being seen for other tests required in the main part of this study. You will be asked to provide about 3 teaspoons of blood and about 3 teaspoons of urine at the following time points: before treatment and 3 months from the time you start treatment.

The research that may be done with your blood and urine is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood and urine will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the blood and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your blood and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood and urine. Then any blood or urine that remains will be returned to your doctor/institution.

In the future, people who do research may need to know more about your health. While the doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood and urine will be used only for research and will not be sold. The research done with your blood and urine may help to develop new treatments for cancer and other diseases in the future.

Benefits

The benefits of research using blood and urine include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ [IRB's phone number].

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
 - Blood Yes No
 - Urine Yes No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
 - Blood Yes No
 - Urine Yes No

3. Someone may contact me in the future to ask me to take part in more research.
 Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II

STUDY PARAMETER TABLE:

PHASE II COMPONENT

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 II

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

APPENDIX III

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 IV

RTOG 0631 Neurological Examination

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

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C1	C2	C3	C4	C5	C6	C7	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>													
L1	L2	L3	L4	L5		sacrum													

2. Radiculopathy (If present, mark all levels)

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C1	C2	C3	C4	C5	C6	C7	C8		T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>															
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		

<p><u>Modified MRC grade of muscle strength</u></p> <p>5 Normal strength</p> <p>5- Equivocal, barely detectable weakness</p> <p>4+ Definite, but slight weakness</p> <p>4 Able to move against gravity with resistance</p> <p>3 Able to move against gravity without resistance</p> <p>2 Active movement without gravity</p> <p>1 Flicker or trace of movement.</p> <p>0 No palpable muscle contraction</p>
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Continued on next page

APPENDIX IV (Continued)

RTOG 0631 Neurological Examination

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 V (11/6/09)

BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:

- Twelve (12) 1 ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN 3373 Sticker
- UN 1895 Dry Ice Sticker

Serum (if requested):

- £ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, 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 3000g at 4° Celsius for 30 minutes.
3. Aliquot 0.5-1 ml serum into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected, and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and store serum frozen until ready to ship. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (If requested):

- £ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, 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 3000g at 4° Celsius for 30 minutes.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
4. Carefully pipette and aliquot 0.5-1 ml plasma into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”.
5. Place cryovials into biohazard bag and store plasma frozen until ready to ship. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buffy coat (if requested):

For a visual explanation of Buffy coat, please refer to the diagram below.

- £ Using one (1) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “buffy coat”.

Process:

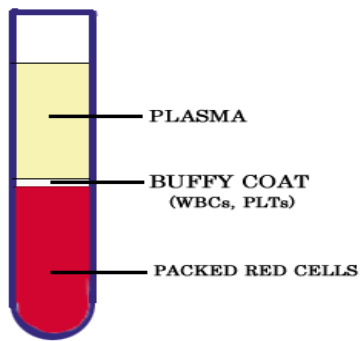
1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).

(continued on next page)

APPENDIX V (Continued)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

4. Remove the buffy coat cells carefully and place into cryovials labeled "buffy coat" (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date/time of collection and time point collected.
5. Place cryovials into biohazard bag and store buffy coat frozen until ready to ship. See below for storage conditions.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Storage:

- £ 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 (please ship out on Monday-Wednesday only).
 - OR:**
 - § Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).
- £ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

*RTOG labels are obtained at the time of patient registration. **PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

Shipping/Mailing:

- £ Include all RTOG paperwork in pocket of biohazard bag.
- £ Ship specimens overnight Monday-Wednesday. (Monday-Tuesday for Canada). Avoid shipping on a weekend or around a holiday.
- £ Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label 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 still plenty of space for 10 lbs of dry ice.*

Ship: Specimens and all paper work as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

APPENDIX VI (11/6/09)

URINE COLLECTION KIT INSTRUCTIONS

This Kit contains:

- One (1) Sterile Urine collection cup
- Biohazard bags

Urine Specimens:

Preparation for collecting **Urine**:

- A clean catch urine specimen will be collected.

Process:

- 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
 - Place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimen as "urine".
- If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
- Place urine cup into biohazard bag and seal the bag
- Store specimens frozen at -20°C or -80°C until ready to ship.

Shipping Instructions for all specimens:

Urine Specimens: Urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Urine specimens may be sent in batches, if within 30 days of collection. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs. minimum). Seal the box with plastic tape. All paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box. **Note:** Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box "biohazard".

Send specimens by overnight express to the address below. Specimens should be shipped Monday through Wednesday only to prevent thawing due to delivery delays. Saturday or holiday deliveries will not be accepted. Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send another sample, collected as close as possible to the original planned collection date.

Notes:

- § Include all RTOG paperwork in pocket of biohazard bag.
- § Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature).
- § *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.*

Ship specimens and all paper work as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu