Phase II Study of Stereotactic Body Radiation Therapy and Vertebroplasty for Localized Spinal Metastasis

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INDEX

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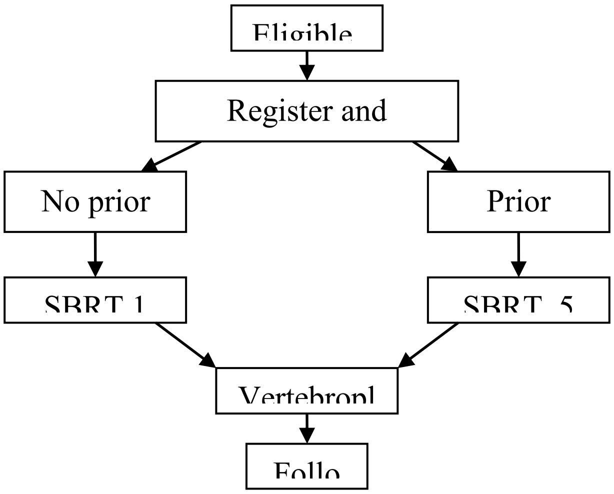
Schema:



Number of patients: 29 patients for 1 fraction treatment having no prior radiation to the treatment site.
13 patients for 5 fraction treatment having a history of prior radiation to the treatment site.

Follow-up Assessment

- VAS[2] of treated spinal level at 2 weeks, 1, 3, and 6 months and then every 6 months for 3 years.
- Patient pain diary of maximum VAS of treated spine recorded once a week on the same day of radiation treatment for 5 weeks following radiation treatment.
- Clinical and neurological exams at 1, 3, 6, and then every 6 months for 3 years
- BPI, Fact-G, and EQ-5D at baseline, 1, 3, 6, and 12 months.
- MRI at baseline 1, 3, 6 and then every 6 months for 3 years.

Eligibility:
Inclusion:

- Patients must have localized spine metastasis (a solitary spine metastasis; two contiguous levels, or up to three separate single vertebral levels are permitted)
- Patients must have a VAS of ≥4 at any of the planned treatment sites
- Patient with epidural, spinal nerve, and/or cord compression on MRI may be included
- Histologic confirmation of cancer is required by biopsy, prior surgery, or re-biopsy
- Narcotic pain prescription and usage information must be available and documented
- Patients must sign study specific consent
- Above the age of 18
- For women of childbearing age a negative pregnancy test is required
- Patients considered for the retreatment arm, must not of had prior radiation to the proposed spinal site within a 3 month interval prior to treatment
- Zubrod score of 0-2

Exclusion:

- Patients who have been non-ambulatory for more than 7 days
- Patients with compression fractures

- Spine instability requiring fixation
- Patients with paraspinal extension
- Patients with bony fragments
- Planned systemic treatment within one week after treatment.
- Absence of pathological diagnosis of cancer
- Chemotherapy within one week of treatment
- Patients with Multiple Myeloma, Lymphoma, or Plasmacytoma
- Patient suffered from unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Patient had a transmural myocardial infarction within the last 6 months
- Patient has an acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Patient has hepatic insufficiency resulting in clinical jaundice and/or coagulation defects
- PT is not within normal limits or planned and feasible to be corrected to normal limits prior to vertebroplasy
- PTT is not within normal limits or planned and feasible to be corrected to normal limits prior to vertebroplasy
- Platelet count is < 50,000
- History of significant psychiatric illness

[1]Vertebroplasty may not be possible for certain patients due to tumor location or safety. In such cases, patients will omit the vertebroplasty but receive all other protocol care and follow-up.
[2]Visual Analog Scoring

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Patient Initial: ________

Eligibility Checklist:

____(Y) 1. Does patient have localized spine metastasis (a solitary spine metastasis; two contiguous levels, or up to three separate single vertebral levels are permitted)?

____(Y) 2. Does patient have a Visual Analog Scoring of pain ≥4 at any of the planned treatment sites within 14 days of registration?____(Y) 3. Was a MRI or CT done? (Patient with epidural, spinal nerve, and/or cord compression on MRI/CT may be included)

___(N) 4. Does patient have paraspinal extension?

____(Y) 5. Did patients sign study specific consent form?

____(Y) 6. Is patient above the age of 18?

____(Y) 7. Does patient have a negative pregnancy test if she is at childbearing age?

____(Y) 8. Does patient have normal vertebral height?

____(N) 9. Did patient have prior radiation to the proposed spinal site within a 3 month interval prior to treatment if patient is considered for the retreatment arm?

____(Y) 10. Is Zubrod performance status 0-2?

____(N) 11. Has patient been non-ambulatory for more than 7 days?

____(N) 12. Does patient have spine instability requiring fixation?

____(N) 13. Is there absence of pathological diagnosis of cancer?

____(N) 14. Did patient receive chemotherapy within one week of treatment?

____(N) 15. Does patient have Multiple Myeloma, Lymphoma, or Plasmacytoma?

____(N) 16. Does the patient have a history of significant psychiatric illness?

____(N) 17. Has the patient suffered from unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?

____(N) 18. Has the patient had a transmural myocardial infarction within the last 6 months?

____(N) 19. Did the patient have an acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?

____(N) 20. Has the patient had hepatic insufficiency resulting in clinical jaundice and/or coagulation defects?

____(Y) 21. Is PT within normal limits or planned and feasible to be corrected to normal limits prior to vertebroplasy?

____(Y) 22. Is PTT within normal limits or planned and feasible to be corrected to normal limits prior to vertebroplasy?

____(Y) 23. Is platelet count ≥ 50,000?

____(Y) 24. Is narcotic pain prescription and usage information available?

The Eligibility Checklist must be completed in its entirely prior to 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 audit.

Completed by ____________________ Date _____________

1.0 **Introduction**:

1.1 Background:

Each year, more than 100,000 patients in the U.S. develop bone metastasis from spread of their primary cancer [1]. Bone is the third most common site of metastatic disease after liver and lung. While all bones can be affected, the most common site of disease spread is the spine. Complications from this metastatic spread include bone pain, pathologic fracture, and spinal cord compression which are associated with considerable morbidity. The incidence of bone metastasis is expected to increase over the next decade as patient survival improves due to advances in anticancer therapy [2]. This will make the treatment of this problem more important in the overall management of the surviving cancer patient.

1.2 Stereotactic Radiation Therapy:

'Stereotactic radiosurgery' generally refers to a radiotherapy procedure designed to treat deep-seated brain tumors or abnormalities, and is commonly performed on a specialized machine, such as the Gamma Knife. This procedure involves immobilizing the patient (cranial halo), affixing a stable 3-D coordinate system (fiducial box and head frame), performing high resolution imaging (CT or MRI), registering the images to the coordinate system using a computer, virtually simulating delivery of very focal and conformal dose profiles of radiation with steep dose gradients toward normal tissue, and finally carrying out the treatment with sub-millimeter accuracy. Typically very high doses of radiation (15-40 Gy) are given in a single treatment with this technique. Any adjacent normal tissues that receive this dose may be significantly damaged, thus the requirement for very conformal treatments with rapid dose fall-off. An alternate strategy has been to divide total radiation dose into 2-5 fractions, still with fairly large dose per fraction (5-10 Gy), attempting to decrease adjacent normal tissue toxicity. These fractionated techniques are referred to as 'stereotactic radiotherapy,' and are carried out with hope that surrounding normal tissue will tolerate the treatment as a result of relatively more successful sublethal damage repair as compared to tumor.

Translation of the stereotactic radiosurgery and radiotherapy concepts to extracranial sites has not been straightforward[4-6]. With brain treatments, the skull serves as an excellent surface to rigidly couple the immobilization frame using stainless steel pins under local anesthesia. Once the skull is immobilized, targets within the skull are likewise immobilized in that there is very little movement of intracranial structures outside of fluid waves around the ventricles. Such is not the case for extracranial soft tissue sites. Inherent motion, such as the heart beating, lungs expanding and emptying, and bowels churning results in movement of potential targets. In addition, the external surface anatomy does not have structures amenable to rigid fixation to a frame. In 1994, Lax, et al, from the Karolinska Hospital in Sweden reported on the development and testing of an extracranial frame that incorporated a fiducial stereotactic coordinate system along its side panels[6]. The system used vacuum pillows to make contact with three sides of the patient (maximizing surface area of contact) and correlation of external anatomical reference points on the sternum and calf. The spine is an ideal site for extracranial stereotactic radiosurgery in one fraction or stereotactic radiotherapy in 3-5 fractions. The bony anatomy of the spine can be visualized with kV imaging such as orthogonal pair x-rays or cone beam CT on today modern radiation treatment machines. The vertebral bones can serve as an internal fiducial for highly precise treatments. The spine is also not prone to movement when immobilization devices are used and the patient is positioned supine [7-10].

Stereotactic body radiation therapy (SBRT) is a new therapeutic paradigm for treating localized tumors outside of the central nervous system and involves delivering very high doses of focused radiation using unique beam arrangements and special immobilization equipment[11]. As already demonstrated in lung and liver cancers, these treatments offer hope for improved local control of cancers that may translate into gains in survival especially for smaller early stage lesions. SBRT employs daily treatment doses dramatically higher than typical for conventionally fractionated radiation therapy (CFRT). In turn, it is incorrect to assume that SBRT radiobiology is similar to historical CFRT. Indeed, a unique biology of radiation response for very large dose per fraction treatments is being appreciated both in terms of tumor control as well as normal tissue consequences translating into unique clinical outcomes. For example, local control with CFRT in early stage lung cancer is consistently reported below 50% while several series using SBRT show local control around 90%[19, 20]. Similarly, high control rates with SBRT for spinal metastases have been demonstrated in large series from Memorial Sloan Kettering, University of Pittsburg, and Henry Ford Hospital [14-16]. The University of Pittsburg has the largest published series of 500 patients treated with single fraction stereotactic radiotherapy for spinal metastasis with local tumor control rates of 90% and long term pain improvement rates of 86% [15].

The radiation dose that can be delivered stereotactically to vertebral body metastasis is limited by the surrounding normal tissues. The spinal cord is the most important organ to consider. Henry Ford Hospital treated 49 patients with spine metastases on a dose escalation protocol allowing a maximum of 10 Gy in a single fraction to 10% of the cord defined 6mm above and below the vertebral body[16]. This was found to be a well tolerated and safe constraint. A radiation dose-response relationship for pain control has not been clearly established. Large radiosurgical experiences have been reported with improved control with higher doses regardless of histology. Both large series from Henry Ford Hospital and University of Pittsburg have shown excellent results with minimal toxicity up to 20 Gy in a single fraction[15, 16]. In patients that have received prior radiation to the spine less is known about the optimal tolerated dose. Bilsky et al. has reported safely giving 20 Gy separated over 4-5 treatments[14]. This protocol will deliver 14-20 Gy in a single fraction to patients that have not received prior radiation in the area and 14-20 Gy in 5 fractions to patients that have received prior radiation treatment to the affected level.

1.3 Vertebroplasty:

Currently, the management of metastatic spinal tumors in the neurologically intact patient includes radiotherapy alone or a combination of surgery and radiotherapy for tumor suppression, pain reduction, and spinal stabilization[17]. Extensive surgical treatment is often limited by a patient's poor general condition, the multifocal nature of the disease, or the patient's short life expectancy. Radiation therapy alone does not impart early spinal stability and, frequently, patients progress to develop further vertebral body height loss or progressive deformity[18]. Percutaneous vertebral augmentation procedures can be effective in preventing further vertebral body collapse and in improving pain relief.

Percutaneous Vertebroplasty (PV) is a minimally invasive fluoroscopically guided procedure aimed at augmenting the vertebral body by injection of polymethyl methacrylate (PMMA) Initially developed in France in the late 1980's to treat aggressive vertebral angiomas, vertebroplasty has gained widespread acceptance worldwide[19]. In the United States, it is predominantly used to treat osteoporotic compression fractures. Percutaneous kyphoplasty is a modification of PV. It involves the percutaneous placement of balloons into the vertebral body, followed by an inflation/deflation sequence to create a cavity prior to the cement injection. The PK procedure may restore VB height and reduce kyphotic angulation prior to PMMA injection[20].

Vertebroplasty has been shown to be effective in controlling pain secondary to compression fractures in over 90% of patients in prospective studies[21]. Significant improvement in quality of life and decreased oral analgesic usage has also been shown. Although not widely used in the United States, vertebroplasty for metastatic spine disease has been shown in multiple studies to be effective in controlling pain and improving quality of life. In one study, 97% of patients experienced decrease in pain within 48 hours of the procedure. In another study 73% of patients decreased their oral analgesic dose by 50% or more[22-25].

The initial complication rate of vertebroplasty in patients with metastatic disease is reported to be approximately 10%[23]. This is significantly higher that observed when the procedure is done for osteoporotic compression fractures (2-5%). This is likely secondary to increased bony destruction in the cancer patient. Reported complications include cement leakage into the spinal canal, neural foramina or paraspinous soft tissue. Notably, most cement leaks are asymptomatic and the long term complication rate is reported to be 1.7%. Cement leakage into the neural foramina can cause a painful radiculopathy which typically improves spontaneously in most patients. Extravasation into the spinal canal can cause spinal cord compression. In some instances surgery to decompress the neural structures was necessary. Extravasation into the epidural venous plexus or inferior vena cava can result in pulmonary embolism[26]. Increased back pain after the procedure has also been reported and is thought to be secondary to local irritation from the PMMA. This typically responds well to a short course of non-steroidal anti-inflammatory medications[25].

1.4 Rationale for Current Protocol

Spinal metastases are a common problem with unique clinical considerations. Indications for treatment of spinal metastases include pain, spinal cord compression, fracture, and spinal instability. The most common is pain. Conventional palliative radiation treatments to the spine gave a pain response rate of approximately 50% at one month according to RTOG 97-14[27]. Stereotactic radiation treatment of spinal metastases has demonstrated a pain response of approximately 80% at one month and has shown tumor control of 88% in the largest single series[15]. This improved local control could be the reason for the durable pain responses. Tumor control has even translated to improvement of neurological symptoms as seen in the trial done at Henry Ford Hospital[28].

The rational for stereotactic radiotherapy of the spine goes beyond the excellent pain response rates and neurological improvement. The primary treatment for patients with metastatic disease is systemic therapy. This therapy often decreases blood counts necessitating expensive supportive measures. Stereotactic radiotherapy can spare spinal bone marrow where much of an adult's blood products are made. This is done by only treating the involved vertebral bone. It has been shown with this method that the risk of failure in adjacent vertebral bones is less than 5%[29]. Next the treatment is convenient and quick allowing patients to come for 1-4 treatments instead of 10-15 treatments. While the patients like this, it is also to their benefit because they can return to systemic therapy quicker. Lastly, stereotactic radiation treatment is non-invasive. Recovery time from stereotactic radiation treatment is short and patients are often able to continue with their daily routines after treatment or the next day.

Radiation causes osteopenia and bone loss [30-33]. While disruption of the destructive growth potential of malignant spinal lesions afforded by radiotherapy is at first helpful, this radiation induced osteopenia becomes counterproductive, especially with time from treatment. Vertebroplasty is a minimally invasive procedure that fortifies bone by injection of polymethyl methacrylate and is indicated in patients with pain from benign and malignant compression. Since radiation to the spine contributes to osteopenia that could lead to destabilization or fracture, vertebroplasty may prevent this late radiation effect. Unfortunately, vertebroplasty may not be technically possible in certain patients due to inability to safely inject the cement. For example, in some cervical spine locations, the vertebral arteries prohibit an approach through the pedicles. Such levels, however, are less likely to undergo post radiation collapse. As such, if it is not technically feasible to perform vertebroplasty, patients may still benefit from SBRT.

This study proposes combining stereotactic body radiation with vertebroplasty to provide both durable local tumor control and pain control while preventing fracture, spinal destabilization, or spinal cord compression.

The hypothesis of this study is stereotactic radiation treatments combined with vertebroplasty will increase pain relief at one month to 80% compared with conventional historical controls of approximately 50% in the setting of patients with no prior radiation treatments and for the group of patients with a history of prior radiation stereotactic radiation combined with vertebroplasty will increase the pain relief at one month to 75% compared with conventional historical retreatment control of approximately 35% .

1.5 Quality of Life (QOL) measurements:

Patients with spinal metastasis have unique clinical considerations. Focal treatments such as radiation are often used to palliate or prevent symptoms such as pain, decreased mobility, fracture, and spinal cord compression. QOL measurements have very important clinical implications since our therapy is directed at improving subjective symptoms such as pain. Improved understanding of patient's symptoms and perceptions of treatment will guide what treatments are most advantageous in the future.

1.5.1 Visual Analogue Scoring System (VAS):

The VAS is a simple measure of pain in 11 scales (0-10). In the study comparing the reliability and validity of several measures of pain intensity, the composites of 0-10 ratings was useful practically when maximal reliability is necessary in studies with relatively small sample sizes or in clinical settings where monitoring of changes in pain intensity in individuals is needed[34].

1.5.2 Brief Pain Inventory (BPI):

Pain originating form the spine affects a patient's quality of life, because the spine is the major weight-bearing area. The BPI is a 17 item patient self rating scale assessing demographic, medication, and pain data. The BPI includes items that will address components of sensory pain including severity, location, chronicity, and degree of relief due to therapy. The BPI includes items that will address components of reactive pain such as depression, suffering, and the perceived ability of relief. The scale is from 0-10, mild pain correlates with scores of 1-4, moderate pain with 5-6, and severe pain with scores of 7-10. Reliability has been demonstrated using the test retest item correlation (eg., for worst pain r = 0.93). As these patients disease progresses, the BPI will be a valuable tool to access the general pain status. Issues of the BPI validity and reliability have been examined in detail[34, 35]. The BPI's ease of translation and brief administration (5 min) have made it a frequent used clinical tool in clinical trials where reduction or prevention of pain are the outcomes measured.

1.5.3 Functional Assessment of Cancer Therapy (FACT-G, version 4.0):

The FACT-G is a commonly used tool for measuring the multidimensional components of health related quality of life (HRQOL) over four scales: physical well being (7 items), social/family well-being (7 items), emotional well being (6 items), and functional well being (7 items)[36]. FACT developed by Cella et al., is a five point 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, all patients can complete the FACT-G in 5-10 minutes. The FACT has been translated into more than 25 different languages.

1.5.4 EuroQol – 5 Dimension (EQ-5D):

The EQ-5D is a method for obtaining evaluations of health related QOL, preference and utility scores to be used as an adjustment to survival, and may be used in future cost-utility analysis. It is a two-part questionnaire that takes approximately 5 minutes to complete[37]. The first part consists of 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 five dimensions, generating 243 (35) health states to which unconsciousness and death are added[38]. The second part is a visual analogue scale valuing current health state measured on a 20 cm 10 point-interval scale. Best imaginable health state is scored as 100 at the top. Both the five-item index score and the Visual analogue scale are transformed into a utility score between 0 "worst health state" and 1 "best health state". Either the index score or the visual analogue score can be used in the quality adjusted survival analysis, or enter the cost utility equation, depending on the health state(s) of interest[39]. Quality-adjusted survival time [U=sum of quality (qi) of health states K times the duration (si) spent in each health state][40]. The EQ-5D has been translated into multiple languages which are available at http://www.euroqol.org/.

2.0 Objectives:

2.1 Primary: To determine the efficacy of stereotactic body radiation for spinal metastasis in reduction of pain at one month. Both partial and complete response will be measured by the visual analogue system (VAS). Partial relief equals an improvement of 2 points on the VAS and complete pain response is defined by a score of 0-1 on the VAS with no increase in narcotic requirement.

2.2 Secondary:

2.2.1 To determine the duration of pain response at the treated site(s) scored as the time of maximal pain relief to an increase of 2 on the VAS

2.2.2 To determine the functional preservation of improvement using the Brief Pain Inventory (BPI)

2.2.3 To prospectively assess patients quality of life (QOL) using the Functional Assessment of Cancer Therapy – General (FACT-G) and patients utilities using the EuroQol (EQ-5D)

2.2.4 To determine the long term stability of the treated vertebral bone (such as fracture, sclerotic change, vertebral body height or mal alignment) by MRI, CT scan and plain radiographs.

3.0 Patient Selection:

3.1 All patients must be willing and capable to provide informed consent to participate in the protocol.

3.2 Histologic confirmation of cancer will be required by biopsy, prior surgery, and re-biopsy at the discretion of the treating physician.

3.3 The patient's Zubrod performance status must be 0-2

3.4 Patients must be or have been ambulatory within a week prior to treatment.

3.5 Patients with instability of the spine requiring instrumentation as judged by a neurosurgeon are not eligible.

3.6 No planned systemic treatment is allowed within one week after treatment.

3.7 Patients must have localized spinal metastasis. This includes patients with a solitary lesion, a lesion that spans two contiguous levels, a lesion with a para-spinal component, and up to three separate single vertebral levels.

3.8 Patients with loss of normal vertebral height, due to for example compression fracture or other process, prior to treatment are not allowed. Patients with normal height and compression fracture are allowed.

3.9 Patients with prior fractionated radiation to the treated site are allowed. Their prior treatment plan with date, fractionation, dose and treatment fields must be obtained. There must be at least a three month interval elapsed from the prior radiation to the treated site and enrollment.

3.10 Patients must have had a visual analog scoring of pain ≥4 at the planned treated site within 14 days of registration. Pain must be ongoing or require narcotic pain medicine to control.

3.11 Narcotic pain prescription and usage information must be available and documented.

3.12 Radiation sensitive histology such as lymphoma, myoloma, or plasmacytoma are not allowed.

3.13 Patients must be past their 18th birthday at time of registration.

3.14 Women of childbearing age must have documentation of a negative pregnancy test and agreed that they or their partner use an effective contraceptive method such as condom/diaphragm and spermacidal foam, non-stainless-steel intrauterine device, or prescription birth control pills.

3.15 Patients should not have a history of significant psychiatric illness.

3.16 Patients should not have severe, active co-morbidity that would preclude vertebroplasty or stereotactic radiotherapy, defined as follows:

3.16.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months.

3.16.2 Transmural myocardial infarction within the last 6 months.

3.16.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.

3.16.4 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects.

3.17 Laboratory entry criteria:

3.17.1 PT within normal limits or planned and feasible to be corrected to normal limits prior to vertebroplasy.

3.17.2 PTT within normal limits or planned and feasible to be corrected to normal limits prior to vertebroplasy.

3.17.3 Platelet count must be ≥ 50,000.

3.18 Patient with epidural, spinal nerve, and/or cord compression on MRI may be included.

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

4.1.1 History and physical exam to include: determination and description of pain from spine metastasis and full neurological exam, VAS for given painful area, BPI, FACT-G, and EQ-5D.

4.1.2 Zubrod performance status (Appendix III).

4.1.3 Imaging studies to include: complete spine MRI and plain radiographs of involved areas

4.1.4 Laboratory work to include: complete blood count with platelets and differential within 30 days or after last round of chemotherapy, Electrolytes, BUN and creatinine as appropriate for histology

4.2 Highly Recommended Evaluations/Management

4.2.1 Dedicated spine CT if clinically indicated or radiographic correlation is needed to evaluate the vertebral body cortex and look for bone fragments within the spinal canal.

5.0 REGISTRATION PROCEDURES

5.1.1 Preregistration Requirements for diagnostic pathology review

There are no requirements for central review of pathology used for initial diagnosis.

5.1.2 Pre-Registration Requirements for SBRT Treatment Approach

In order to utilize SBRT in this protocol, the institution must have met technology requirements and have provided a description of techniques, methods, training, and experience showing competency to the study PIs.

5.2 Registration

5.2.1 Fax Registration

Prior to registration, participating investigators and institutions should review the eligibility checklist and confirm eligibility. Patients can be registered only after eligibility criteria are met. To register a patient, the site should fax the Enrollment Form to the Project Manager (fax #: 214-648-5923). A unique, participant ID number will then be assigned.

5.3 Accreditation

5.3.1 Institutional Processes

Prior to treating patients on protocol, the institution's specific methods for immobilization (e.g., frame vs. frameless), targeting, dose construction, daily verification of accuracy, ongoing assessment of accuracy and Quality Assurance policies must be described to and approved by the study PI and other approved institutional PIs. The primary purpose of accreditation will be to insure that dose is delivered to the targets and avoiding normal tissues according to protocol criteria. This accreditation may be assessed by written documentation, conference calls, or direct observation via site visits. Additional data may be required of institutions to verify that techniques are performing as intended.

6.0 RADIATION THERAPY

6.1 DOSE SPECIFICATIONS

6.1.1 Stereotactic Targeting and Treatment

The term "stereotactic" for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space guided by one or several fiducials of known 3-D coordinates. This differs from conventional radiation therapy in which therapy is directed toward skin marks or bony landmarks and assumed to correlate to the actual tumor target based on a historical simulation. It should be understood that Stereotactic Body Radiation Therapy (SBRT) has become a treatment that is well beyond just stereotactic targeting. Indeed SBRT is mostly about ablative range dose per fraction, accounting properly for errors including motion, careful construction of dosimetry that delivers high dose to the tumor and not normal tissues, and extra careful treatment delivery. This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward a target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radio-opaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor/spine itself as a fiducial (e.g. acquiring tomographic views of the tumor simultaneously with the treatment).

6.1.2 Dose Fractionation

Patients will be treated by two different dose fractionation schedules decided by a prior history of radiation to the treated area. Patients with no prior treatment will receive a single fraction of radiation. Each patient will have two target volumes of interest regardless of fractionation, a Planning Treatment Volume (PTV) and a Gross Tumor Volume (GTV) defined below. Minimum prescription dose for the single fraction treatment will be 14 Gy to at least 95% of the PTV and 20 Gy to at least 90% of the GTV. The plans overall maximum dose must occur within the GTV and be no greater than 25 Gy. For the single dose regimen, the spinal cord will receive no greater than 14 Gy to a point, 10 Gy to no more than 0.25 cc of spinal cord volume, and 7 Gy to no more than 0.5 cc of spinal cord volume. Patients with prior radiation treatment will be treated with 5 fractions of radiation. A minimum of 14 hours and a maximum of 7 days should separate each treatment. Minimum prescription dose for the five fraction treatment will be 2.8 Gy per fraction to at least 95% of the PTV for a total dose of 14 Gy and 4 Gy per fraction to at least 90% of the GTV for a total dose of 20 Gy. The plan's overall maximum dose must occur within the GTV and be no greater than 5 Gy per fraction for a total dose of 25 Gy. For the five fraction retreatment regimen, the spinal cord will receive no greater than 14 Gy (2.8 Gy per fraction) to a point, 10 Gy (2 Gy per fraction) to no more than 0.25 cc of spinal cord volume, and 7 Gy (1.4 Gy per fraction) to no more than 0.5 cc of spinal cord volume. Treatment dose will prescribed typically to the 70-90 percent isodose line for each fractionation scheme.

Total doses will be the same for the single fraction and five fraction treatments

Structure	Dose	Required Volume	Minor Volume Variation	Major Volume Variation	Required Conformality index (CI)
PTV	≥ 14 Gy	≥ 95%	90% - 95%	< 90%	1.3
	≥ 12.6 Gy	≥ 99%	95% - 99%	< 95%	
GTV	20 Gy	≥ 90%	85% - 90%	< 85%	

6.1.3 Premedications

Unless contraindicated, it is recommended but not required that all patients receive corticosteroid premedication (e.g. Decadron 4 mg p.o. in a single dose, or equivalent) 15-60 minutes prior to each of the five treatments for the intended purpose of modulating immediate acute inflammatory effects. Analgesic premedication to avoid general discomfort during long treatment durations is also recommended when appropriate.

6.1.4 Supportive medicines

Are allowed as medically indicated.

6.2 Technical Factors

6.2.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators with photon energies 6-21 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed.

6.2.2 <u>Dose Verification at Treatment</u>

Personal dosimeter measurements (e.g. diode, TLD, etc.) may be obtained for surface dose verification for accessible beams as per institutional preference. This information is not required by the protocol.

6.3 Localization, Simulation, and Immobilization

6.3.1 <u>Patient Positioning</u>

Patients will be positioned supine in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system. All positioning systems must be validated and accredited by the Study Committee (Principal Investigator and Institutional PIs) prior to enrolling or treating patients on this trial. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.2 <u>Inhibition of Effects of Internal Organ Motion</u>

Special considerations must be made to account for the effect of internal organ motion (i.e., breathing, etc.) on target positioning and reproducibility. In some cases, the intrafractional tumor motion is small and no special maneuvers are required to achieve motion limits (as is true with most spinal metastasis treated in the supine position). Treating in the prone position will accentuate internal organ motion problems related to breathing and should be avoided unless special measures are taken to account for this motion. When accounting for intrafractional motion, acceptable maneuvers including accelerator beam gating or tracking with the respiratory cycle, and active breath-holding techniques. Internal organ inhibition maneuvers must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%). Assessment of this motion will be left to the institution. This type of interfractional motion analysis with correction is only required by protocol just prior to each separate treatment. Intrafraction assessment during the course of each treatment (dynamic and adaptive maneuvers) is allowed and encouraged especially if treatment times are long.

6.3.3 <u>Localization and treatment maneuvers</u>

A direct method of localization of the spine on the day of treatment must be used in this protocol. Acceptable methods would include placing a radio-opaque seed or marker that can be visualized and triangulated using dual imaging prior to simulation and planning. Also, it would be acceptable to perform computed tomography such as axial, spiral or conebeam CT prior to each treatment in the treatment position to identify the tumor target directly. Orthogonal kv or mv x-ray images (or patients should undergo a tomographic imaging study utilizing the linear accelerator couch, if available) should be obtained on the day of treatment and compared to digitally reconstructed images from simulation to ensure proper alignment.

6.4 Treatment Planning/Target Volumes

6.4.1 <u>Image Acquisition</u>

Computed Tomography (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. Treatment planning images should be performed in the treatment position using all aids/maneuvers described above. Axial acquisitions with gantry 0 degrees will be required with spacing $\leq$ 2.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

Image fusion with other imaging modalities such as MRI that might be useful in delineating the target and normal tissues is encouraged. MRI is to be done in the treatment position to allow for precise fusion.

6.4.2 Target Volumes

The GTV (gross tumor volume) will be defined as gross tumor visualized on CT/MRI scan in the vertebral body, para-spinal recess, or in the spinal canal. The CTV (clinical target volume) will include the GTV and contiguous bone marrow cavity adjacent to the tumor. The posterior elements of the vertebra will be included in the CTV only when directly involved by gross tumor. GTV and CTV target volume will be outlined by an appropriately trained physician. The target will generally be drawn using CT soft tissue/bone windows and from fused MRI. Since the spine is very stable and daily image guidance is used there will be no expansion from CTV to PTV. That is, the CTV will also be the PTV (planned target volume).

6.4.3 Dosimetry

Three-dimensional coplanar or non-coplanar beam, arc rotation, or Intensity Modulated Radiotherapy (IMRT) beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, 10-15 beams of radiation will be used with roughly equal weighting for conventional linac treatments. When static beams are used, a minimum of 10 non-opposing beams should be used. For arc rotation techniques, a minimum of 300 degrees (cumulative for all beams) should be utilized. For CyberKnife treatments many more beams may be utilized depending on the size and the location. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e. no additional "margin" for dose build up at the edges of the blocks or MLC jaws beyond the PTV). As such, prescription lines covering the PTV will typically be the 70-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the GTV (COM_{GTV}). 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. Regardless, the point identified as COM_{GTV} must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 70-90%. The prescription dose in both the single fraction and five fraction treatments will be delivered to the margin of the GTV and fulfill the requirements below. As such, a "hot spot" will exist within the GTV centrally at the COM_{GTV} with a magnitude of the prescription dose times the reciprocal of the chosen prescription isodose line (i.e., 70-90%).

For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body should be modeled in the planning system as to their electron density. Proper heterogeneity correction algorithms should be approved by the PI.

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

1) Normalization
The treatment plan should be normalized such that 100% corresponds to the center of mass of the GTV (COM_{GTV}). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams.

2) Prescription Isodose Surface Coverage
The prescription isodose surface will be chosen such that ≥95% of the target volume (PTV) is covered by the minimum prescription isodose surface (see section 6.1.2) and 99% of the target volume (PTV) receives a minimum of 90% of the minimum prescription dose. However, the spinal tolerance limits in section 6.5 should not be exceeded, even if the goals of target coverage remain unmet. In such a case, the treatment should proceed at the attainable dose without exceeding spinal cord tolerance with a potential protocol violation for target coverage.

3) Target Dose Heterogeneity
The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the GTV (COM_{GTV}) and ≤ 90% of the dose at the center of mass of the GTV (COM_{GTV}). The COM_{GTV} corresponds to the normalization point (100%) of the plan as noted in 1) above.

4) High Dose Spillage
   a. Location
   Any dose greater than 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside of the PTV. Therefore, the cumulative volume of all tissue outside of the PTV receiving a dose greater than 105% of prescription dose should be no more than 15% of the PTV volume. Ideally, these hot spots will be manipulated to occur within the gross tumor volume. IMRT and other techniques will be encouraged to accomplish this goal.
   b. Volume
   Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1) through 4) to the volume of the PTV is less than 1.3.

6.5 Critical Structures

6.5.1 Critical Organ Dose-Volume Limits

The following tables lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and dose that exceeds these limits by 5% will constitute a major protocol violation.

These limits were formulated with the approval of the study committee using known tolerance data, radiobiological conversion models, norms used in current practice at academic centers. Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits. The tables list limits for previously non-irradiated tissues. Previous radiation dose should be quantified. Clinicians should factor in previous radiation by modifying the actual dose tolerance limits employed in a given patient on a case by case basis.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow below.

6.5.2 **One Fraction**

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Endpoint (≥Grade 3)**
Brainstem	<1 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord	See section 6.1.2			myelitis
Cauda Equina	<5 cc	14 Gy	16 Gy	neuritis
Esophagus*	<5 cc	14.5 Gy	19 Gy	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	14.4 Gy	16 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	8.8 Gy	22 Gy	stenosis/fistula
Skin	<10 cc	14.4 Gy	16 Gy	ulceration
Stomach	<10 cc	13 Gy	16 Gy	ulceration/fistula
Duodenum*	<5 cc	8.8 Gy	16 Gy	ulceration
Jejunum/Ileum*	<5 cc	9.8 Gy	19 Gy	enteritis/obstruction
Colon*	<20cc	11 Gy	22 Gy	colitis/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)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.4 Gy		Pneumonitis
Liver	700 cc	9.1 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	8.4 Gy		Basic renal function

Five Fractions – These limits for non-irradiated tissues. Clinician must account for previous dose to normal structures using clinical judgement on a case by case basis.

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Endpoint (≥Grade 3)**
Brainstem	<1 cc	26 Gy (5.2 Gy/fx)	31 Gy (6.2 Gy/fx)	cranial neuropathy
Spinal Cord	See section 6.1.2			myelitis
Cauda Equina	<5 cc	30 Gy (6 Gy/fx)	34 Gy (6.4 Gy/fx)	neuritis
Esophagus*	<5 cc	27.5 Gy (5.5 Gy/fx)	35 Gy (7 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	38 Gy (7.6 Gy/fx)	pericarditis
Great vessels	<10 cc	47 Gy (9.4 Gy/fx)	53 Gy (10.6 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	18 Gy (3.6 Gy/fx)	38 Gy (7.6 Gy/fx)	stenosis/fistula
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Stomach	<10 cc	28 Gy (5.6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	18 Gy (3.6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)	enteritis/obstruction
Colon*	<20cc	25 Gy (5 Gy/fx)	38 Gy (7.6 Gy/fx)	colitis/fistula
Renal hilum/vascular trunk	<2/3 volume	23 Gy (4.6 Gy/fx)		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis
Liver	700 cc	21 Gy (4.2 Gy/fx)		Basic Liver Function
Renal cortex	200 cc	17.5 Gy (3.5		Basic renal function

(Right & Left)		Gy/fx)		

***Avoid circumferential irradiation**

6.6 Contouring of Normal Tissue Structures

6.6.1 Spinal Cord

The spinal cord will be contoured as multiple structures based on MRI or CT. Ideally the actual spinal cord and not necessarily the entire spinal canal will be contoured if possible. For each treated site, the spinal cord should be contoured on axial slices in the region of the PTV and extending at least 2.5 cm above and below the PTV. Each section of contoured spinal cord will be evaluated separately.

6.6.2 Cauda Equina

The cauda equina will be contoured as multiple structures based on MRI. For each treated site, the cauda equina should be contoured on axial slices if it is within 5 cm of the PTV. The superior aspect of the cauda equina begins at the conus medularis. The entire spinal canal will be contoured to represent the cauda equine extending inferiorly to the end of the thecal sac.

6.6.3 Lungs

Both the right and left lungs should be contoured as one structure. Contours should be carried out using pulmonary windows on CT. Any para-spinal gross tumor should not be included in this structure.

6.6.4 Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured 5 cm above the superior extend of the PTV and continued on every slice to 5 cm below the inferior extent of the PTV.

6.6.5 Small Intestine

Small intestine will be contoured if the PTV is within the range of T10-L5. The small intestines should be contoured as a conglomerate of all bowel loops within each CT cut starting at the first appearance of small intestine in the pelvis and extending superiorly up to the level of the sacral promontory within each cut.

6.6.6 Kidneys

Kidneys will be contoured if the PTV is within the range of T10-L5. Each kidney should be contoured and evaluated separately. Kidney should be contoured on abdominal windows on CT.

6.6.7 Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for the purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

6.6.8 Skin

The skin will constitute the external contour minus 5 mm. The skin within folds, especially in the gluteal folds as the skin surfaces make contact, will be contoured as a separate structure.

6.7 Documentation Requirements

6.7.1 In general, treatment interruptions 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.

6.8 Compliance Criteria

6.8.1 Accreditation Compliance

All criteria listed in Section 5 must be completed to the satisfaction of the study committee in order to be accredited. Upon completion of the criteria, a letter will be sent to institutions' PIs informing them of accreditation for the study. No institution will be allowed to enroll patients without accreditation.

6.8.2 Dosimetry Compliance

Section 6 describes appropriate conduct for treatment planning dosimetry. The table in Section 6.5 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor protocol violation. Exceeding these limits by more than 5% constitutes a major protocol violation and should be strictly avoided.

6.8.3 Treatment Delivery Compliance

Set-up films will be compared to digitally reconstructed radiographs from the same beam's eye view. Deviations of less than 0.3 cm will be considered compliant. Deviations from 0.3-0.5 cm will be considered minor protocol deviations. Deviations greater than those listed as minor will be considered major protocol deviations.

6.8.4 Target Coverage Compliance

As listed in sections 6.1.2 and 6.4.3, the protocol requires that 95% of the PTV volume be given the protocol dose while 99% of the PTV volume should get 90% of the prescribed dose. A minor violation would be issued for PTV prescription dose coverage of 90-95% while and a major violation for <90%. A minor violation will be issued if between 95-99% of the target volume receives 90% of the prescribed dose, while a major violation for <95% of the volume. In regard to the GTV coverage, a minor violation will be issued for coverage of 85-90% of the volume by the prescription dose, while a major violation for <85% of the volume.

6.9 R.T. Quality Assurance Reviews

Dr. Timmerman will perform an RT Quality Assurance Review after complete data for the first 9 cases enrolled into the single fraction group and 6 patients enrolled into the four fraction group have been received at the University of Texas Southwestern. Dr. Timmerman will perform the next review after complete data for the next and subsequent 15 cases enrolled has been received at the University of Texas Southwestern. 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, whichever occurs first.

6.10 Radiation Adverse Events

6.10.1 Neurology

Monitored treatment related toxicity associated with neurology function will include myelitis, motor and sensory neuropathy, plexopathy, and pain. The consequences of neurology toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.10.2 Blood/Bone Marrow

Monitored treatment related toxicity associated with blood and bone marrow function will include anemia, leukocytopenia, thrombocytopenia, and myelodysplasia. The consequences of blood and bone marrow toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.10.3 Constitutional Symptoms

Monitored treatment related toxicity associated with constitutional function will include fatigue, fever, and weight loss. The consequences of constitutional toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.10.4 Skin

Monitored treatment related toxicity associated with skin function will include fibrosis, rash (desquamation), ulceration, and telangiectasia. The consequences of skin toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.10.5 Gastro-intestinal

Monitored treatment related toxicity associated with gastrointestinal function will include colitis, dehydration, diarrhea, enteritis, fistula, nausea, vomiting, obstruction, proctitis, fecal incontinence, stricture/stenosis, hemorrhage, and ulcer. The consequences of gastro-intestinal toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.10.6 Renal/Genitourinary

Monitored treatment related toxicity associated with renal and genito-urinary function will include cystitis, fistula, urinary incontinence, urinary obstruction, hemorrhage, and urinary retention. The consequences of renal/genitourinary toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.10.7 Quality of Life and Other Toxicities

Other treatment related toxicity attributed to the therapy will be captured, recorded and the consequences of should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE). VAS, BPI, FACT-G and EQ-5D

6.11 Serious Adverse Event Reporting

6.11.1 ERGO

Electronic Research Grant Organizer (ERGO) constitutes a mechanism for reporting serious adverse events to the UTSW IRB for reporting purposes.

Any adverse event equivalent to CTCAE V.3 grade 3, 4, or 5 or which precipitates hospitalization or prolongs an existing hospitalization must be reported regardless of designation (expected or unexpected) along with the attribution. This includes all deaths that occur within 30 days after the patient was discontinued from the study regardless of attribution AND any events that occur beyond 30 days and are considered probably related to treatment.

Participating sub-sites must file an SAE report (the CRF plus information describing the event, the grade, and the attribution) within 48 hours of the investigator's awareness of the occurrence of the event.

Attribution of an event can be categorized as:

- Not Related
- Possibly Related
- Likely Related

Adverse events (below grade 3) do not need to be submitted immediately. Rather, they should be documented in the Adverse Events CRF along with a brief description of the event, grade, and attribution).

All SAE reports should be made via FAX transmission to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Jean Wu, Project Manager
FAX #: 214-648-5923

<u>7.0 Drug Therapy</u>:

Chemotherapy will be held 1 week prior to radiation and may be continued one week after treatment.

<u>8.0 Surgery</u>:

8.1 Vertebroplasty

Vertebroplasty will be performed within one month of start of radiation therapy in the standard angiography suite or in the operating room depending on individual patient needs. C-arm fluoroscopy will be utilized for localization and visualization throughout the procedure. All patients undergo continuous physiologic monitoring and observation by anesthesia provider. In most instances the procedure may be completed using conscious sedation with a combination of a short acting narcotic and benzodiazepine. Local anesthesia with lidocaine or bupivicaine is also utilized.

The patient will be positioned prone on the operating table, prepped and draped in the usual sterile fashion. Under fluoroscopic guidance, the pedicle of the involved vertebral level is localized. The skin, soft tissue and periosteum are anesthetized. A standard bone biopsy needle with an outer cannula and a central stylet is advanced under fluoroscopic guidance into the vertebral body via the pedicle. The stylet is removed and the polymethyl methacrylate (PMMA) mixture is injected into the vertebral body through the cannula under continuous fluoroscopy. Careful attention to any extravasation is noted. After adequate vertebral body fill, the cannula is withdrawn and a sterile dressing applied to the puncture site.

<u>9.0 Other Therapy</u>:

9.1 <u>Permitted Supportive Therapy</u>

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 Antiemetics
- 9.1.2 Anticoagulants
- 9.1.3 Antidiarrheals
- 9.1.4 Analgesics
- 9.1.5 Hematopoietic Growth Factors
- 9.1.6 Herbal products
- 9.1.7 Nutritional supplementation

10.0 TISSUE/SPECIMEN SUBMISSION

10.1 Specimen Collection For Central Review For Eligibility

Central review of pathology is not required for entry on to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 Follow-up Schedule

11.2.1 Initial follow-up visit at 2 weeks then 1, 3 and 6 months from start of treatment.

11.2.2 VAS will be measured at 2 weeks, 1, 3, and 6 months and then every 6 months for 3 years by research staff. VAS will be measured on the day of treatment and weekly there after for 5 weeks by patient diary.

11.2.3 BPI, Fact-G, and EQ-5D will be done at baseline, 1, 3, 6, and 12 months post therapy.

11.2.4 After initial follow-up visits, follow-up will be done at 6 month intervals post therapy for 3 years.

11.2.5 MRI at baseline, 1, 3, 6 and then every 6 months for three years. These MRI are to be done of the treated level and a complete whole spine MRI will be done when clinically indicated based on pain or other new neurological symptom.

11.3 Criteria for Toxicity

11.3.1 All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.

11.4 Measurement of Pain Response

11.4.1 Pain as the primary endpoint of the study will be assessed by VAS at 1 month by research staff.

11.4.2 Pain will also be assessed by VAS at 2 weeks, 1, 3, and 6 months and then every 6 months for 3 years post therapy by research staff. A patient pain diary of maximum VAS of treated spine recorded on the same day of radiation treatment and then weekly for 5 weeks following radiation treatment.

11.4.2.1 Response to pain will be scored as Complete Response (CR), Partial Response (PR), or other.

11.4.2.2 Complete response (CR): defined as a score of 0 on the VAS at the treated site with no increase in narcotic requirements

11.4.2.3 Partial response (PR): defined as an improvement of at least two points on the VAS with no increase in narcotic requirement.

11.4.2.4 Other will include people with stable pain, increasing narcotic requirements, and progressive pain

11.5 Measurement of Tumor Response

11.5.1 Spinal metastasis dimensions in centimeters must be recorded on the data collection forms for the initial and follow-up evaluations of the patient.

11.5.2 After study entry, disease evaluations will be made and recorded using the following Response Evaluation Criteria in Solid Tumors (RECIST):

11.5.2.1 Complete Response (CR): No clinical evidence of disease on CT or MRI imaging.

11.5.2.2 Partial Response (PR): This rating will be assigned when at least a 30% decrease in the maximum single dimension of the target lesion has occurred, taking as reference the baseline maximum dimension of the target lesion

11.5.2.3 Stable Disease (SD)[46]: This rating will be assigned when neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest single dimension measurement since treatment started.

11.5.2.4 Progressive Disease (PD): Progressive disease will be declared when at least a 20% increase in maximum dimension of the target lesion, taking as reference the smallest single dimension measurement since treatment started.

11.6 Other Response Parameters

11.6.1 Duration of Pain Response: The duration of pain response will be measure from the date that CR or PR was recorded to the date of increase in the VAS at the treated site to a score 2 points higher than the lowest VAS score recorded.

11.6.2 Time to Functional Decline: Time from study entry to a Zubrod PS ≤ 3

11.6.3 Overall Survival: The survival time will be measured from the date of accession to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death.

11.7 Removal of Subject from Study

We will be following the patients for 3 years. Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

11.7.1 Subject voluntarily withdraws from consent

11.7.2 Subject is unable to comply with protocol requirements.

11.7.3 Subject demonstrates disease progression to targeted site.

11.7.4 Subject experiences toxicity that makes continuation in the protocol unsafe.

11.7.5 Development of second malignancy that requires treatment, which would interfere with this study.

11.7.6 Treating physician judges continuation on the study would not be in the subject's best interest.

11.7.8. Subject becomes pregnant.

11.7.9 If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up". All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

12.0 DATA COLLECTION

Data should be submitted to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Jean Wu, Project Manager
5801 Forest Park Road
Dallas, Texas 75390-9183
FAX #: 214-648-5923

Patients will be identified only by initials (first middle last) and a unique study ID number assigned to each study participant; 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. Participating sub-sites must remove or black-out identifiers from source documentation that is sent to UTSW.

Study-related data will be stored for 5 years after termination of the study when accrual is no longer taking place and all patients have discontinued follow-up procedures.

12.1 Summary of Data Submission

Item	Recommended Submission Timeline
Demographics	Within 2 weeks of study entry
Eligibility and Entry Characteristics including baseline H&P	Within 2 weeks of study entry
Pathology Report	Within 2 weeks of study entry
QOL studies	Within 2 weeks of study entry
SBRT dosimetry information	Within 1 week after completion of SBRT
Follow-up H&P data	After last SBRT treatment, post SBRT follow-up at 2 weeks, 1, 3, 6, then every 6 months to 3 years
QOL forms post treatment	After last SBRT treatment, post SBRT follow-up at 2 weeks, 1, 3, 6, then every 6 months to 3 years
Adverse Event assessment	After last SBRT treatment, post SBRT follow-up at 2 weeks, 1, 3, 6, then every 6 months to 3 years

12.2 Procedures to Maintain Confidentiality

Patient medical information obtained as a result of this study is considered confidential. Patient data will be kept in a locked file in the Clinical Research Office, and all electronic data will be password protected. All reports and communications related to subjects in this study will identify patients only by his/her initials/number. Organizations that may look at and/or copy medical records for research, for quality assurance, and data analysis include: the Institutional Review Board (IRB – a group of people who review the study to protect patient rights), the FDA, the Office for Human Research Protections (OHRP). These agencies may review the research to ensure that it is done safely and correctly. Patient confidentiality will be maintained at all times unless government regulation or applicable law requires disclosure. The investigators are obtaining a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). This Certificate adds special protections for research information that identifies participants and will help researchers protect subject privacy.

13.0 Statistical Consideration:

13.1 Single Fraction Treatment Group

Two-Stage Design and Sample Size Justification

The planned sample size of 29 total eligible subjects is based on Simon two-stage optimal design with an overall significance level of 0.05 and power of 90% (Simon R, 1989). The concept of this design is to permit early stopping when a moderately long sequence of initial failure occurs. The historical response rate to conventional radiation treatments is 50%[27]. This response rate comes from the RTOG 9714 trial which looked at 800 cGy in one fraction vs 3000 cGy in ten fractions. It represents combined complete and partial responses. This trial set the standard of care for palliation of pain bone metastasis in previously unirradiated patients and thus is used as the historical control for this group. The statistical hypothesis tested is as follows:

H_0: p≤50% vs. H_A: p≥80%, where p is one month pain response rate

Rejection of H_0 means that further study of the test treatment should be carried out. Under the above hypotheses, the type I error is the false-positive rate in accepting an ineffective treatment and type II error is the false-negative rate in rejecting a promising treatment.

Stage 1 of the study will include 9 eligible subjects. If at least 6 of 9 eligible subjects respond, an additional 20 subjects will be enrolled into stage 2 of the study. If the total number of patients who respond (among the 29 patients) is 19 or more, the null hypothesis above will be rejected in favor of the alternate hypothesis.

Under the null hypothesis (p≤50%), the expected sample size of the trial is only 14.

The assumptions and specifications for Simon's two-stage design are detailed in the following table 1
Alpha ---> 0.05
Beta ---> 0.10
Response Probability of Historical Conventional Radiation Treatment (P0) ---> 0.5
Response Probability of Stereotactic Radiation Treatment (P1) ---> 0.8

Table 1. Power Calculation and Sample Size Calculation Table

Optimal Two Stage Design	Optimum Design
First Stage Sample Size (n1)	9
Upper Limit For 1st Stage Rejection of Stereotactic Radiation Treatment (r1)	5
Maximum Sample Size (n)	29
Upper Limit for 2nd Stage Rejection of Stereotactic Radiation Treatment (r)	18
Expected Sample Size If Response Probability = P0	14.08
Probability of Early Termination at P0	0.75

13.2 Five Fraction Treatment Group

Two-Stage Design and Sample Size Justification

The planned sample size of 13 total eligible subjects is based on Simon two-stage optimal design with an overall significance level of 0.05 and power of 90% (Simon R, 1989). The concept of this design is to permit early stopping when a moderately long sequence of initial failure occurs. The historical response rate to conventional radiation treatments is 35%[42]. This response rate comes from a subsequent analysis of the Dutch Bone Metastasis Study which looked at 800 cGy in one fraction vs 2400 cGy in multiple fractions. It represents combined complete and partial responses. This analysis details what the response rate to conventional radiation retreatment in the setting of prior irradiation to the treated area and thus is used as the historical control for this group. The statistical hypothesis tested is as follows:

H_0: p≤35% vs. H_A: p≥75%, where p is response rate

Rejection of H_0 means that further study of the test treatment should be carried out. Under the above hypotheses, the type I error is the false-positive rate in accepting an ineffective treatment and type II error is the false-negative rate in rejecting a promising treatment.

Stage 1 of the study will include 6 eligible subjects. If at least 3 of 6 eligible subjects respond, additional 7 subjects will be enrolled into stage 2 of the study. If the total number of patients who respond (among the 13 patients) is 8 or more, the null hypothesis above will be rejected in favor of the alternate hypothesis.

Under the null hypothesis ($p \leq 35\%$), the expected sample size of the trial is only 9.

The assumptions and specifications for Simon's two-stage design are detailed in the following table 2
Alpha ---> 0.05
Beta --> 0.10
Response Probability of Historical Conventional Radiation Treatment (P0) ---> 0.35
Response Probability of Stereotactic Radiation Treatment (P1) ---> 0.75

Table 2. Power Calculation and Sample Size Calculation Table

Optimal Two Stage Design	Optimum Design
First Stage Sample Size (n1)	6
Upper Limit For 1st Stage Rejection of Stereotactic Radiation Treatment (r1)	2
Maximum Sample Size (n)	13
Upper Limit for 2nd Stage Rejection of Stereotactic Radiation Treatment (r)	7
Expected Sample Size If Response Probability = P0	8.47
Probability of Early Termination at P0	0.65

13.3 Secondary Endpoints

Secondary endpoints will be analyzed by the following methods. For overall survival Kaplan-Meier plots and median times will be reported. Time to functional decline will me measured with Kaplan-Meier plots and median times will be reported. Duration of pain response will be measured with Kaplan-Meier plots and median duration of pain response will be reported.

14.0 Data Safety Monitoring Plan

A data safety monitoring committee including radiation oncologists not participating in this trial will be formed to review toxicity endpoints and efficacy data. The data safety monitoring committee will review and verify all reported AE. In particular, this committee will scrutinize the grading of adverse events and the attribution to therapy previously assigned by the investigators. This panel will have access to patient information so as to have the ability to critically review toxicity events. This study will use this committee to perform ongoing safety assessment. Toxicities will be reported to the treating center's IRB and also to the University of Texas Southwestern IRB.

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Appendix I

STUDY PARAMETER TABLE

	PreTreatment	During Treatment		Follow-Up (months after therapy)			
	Within 30 days of study entry	With each treatment	After last treatment	1	3	6	Every 6 months for three years
Confirmation of Pathology	X						
History/physical	X	X	X	X	X	X	X
Performance Status	X			X	X	X	X
MRI spine*	X[1]			X[1]	X[1]	X[1]	X[1]
CT spine*	X[1]			X[1]	X[1]	X[1]	X[1]
BUN, creatinine, CBC w/ platelets, PT/PTT INR	X						
Informed consent	X						
Tumor response evaluation	X			X	X	X	X
VAS at treated Site	X		X	X	X	X	X
Adverse event evaluation		X	X	X	X	X	X
QOL Studies	X		X	X	X	X	X
(BPI, Fact-G, EQ-5D)	X			X	X	X	(12 months only)
Vertebroplasty		X[2]					

*X[1]: Per physician's discretion
X[2] : within one month of start of radiation treatment.

Appendix II

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).**
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 (Karnofsky 70-80).**
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 (Karnofsky 50-60).**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).**
5	**Death (Karnofsky 0).**

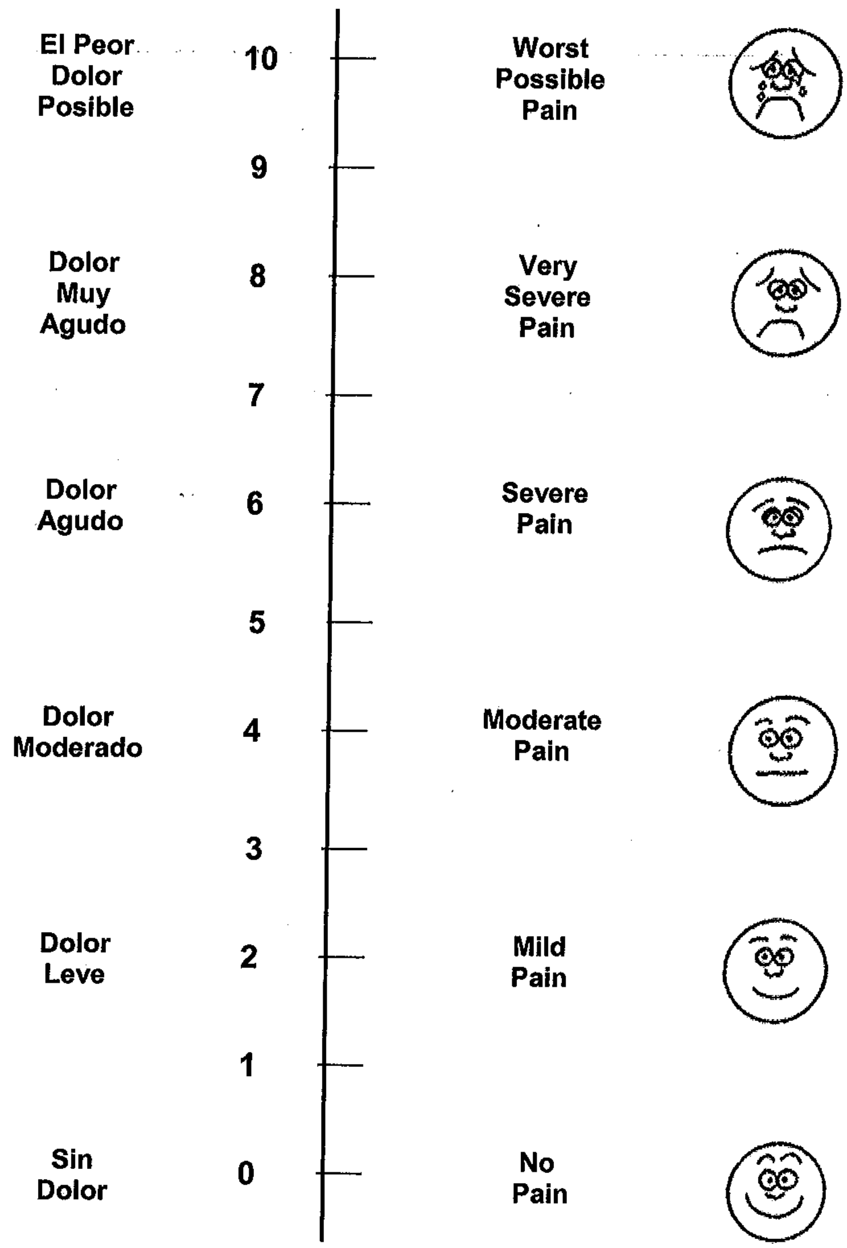
Appendix III

Visual Analog Scoring System (VAS)

Pain slows healing. Help us keep your pain controlled.
We want you to be as comfortable as possible.

El dolor retarda la curación. Ayúdanos a controlar su dolor.
Queremos que se encuentre lo más confortable que pueda.

PAIN INTENSITY SCALE



UT SOUTHWESTERN

Appendix IV
Brief Pain Inventory

STUDY ID# ____________ HOSPITAL # ____________

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

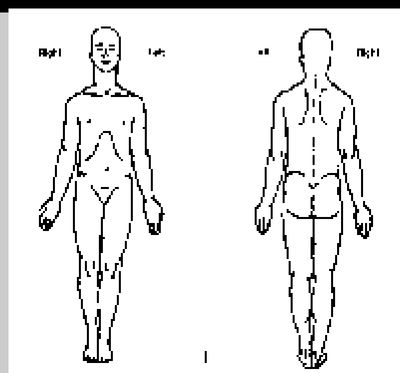
Date: ____/____/____ Time: ____

Name: ______________________ ______________________ ______________________
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much **relief** you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

Appendix V

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix VI

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

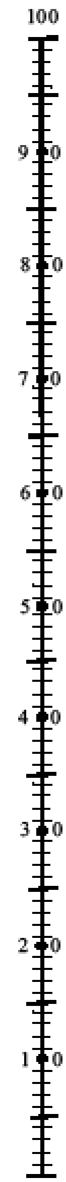
2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Best imaginable health state



Worst imaginable health state