09-RAD-01: Conformal High Dose Intensity Modulated Radiation Therapy for Asymptomatic Metastatic Disease to the Thoracic and Lumbar Spine

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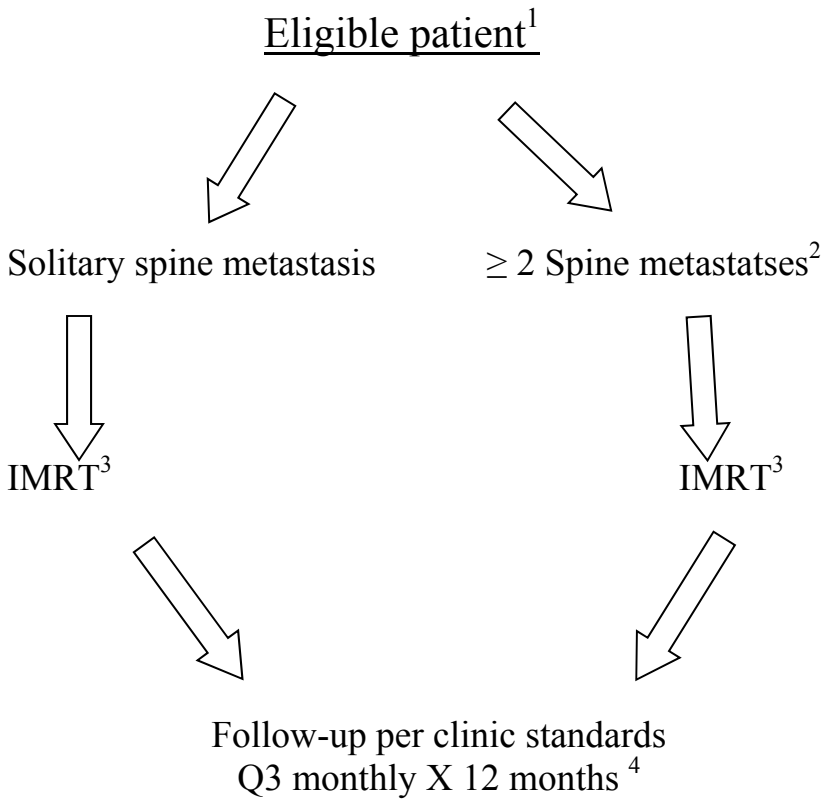
Table of Contents

1.0

Schema



1. Any solid tumor including hormone refractory breast/prostate cancer or lymphoma/myeloma; Asymptomatic spine metastasis by MRI/nuclear medicine scan
2. Single lesion treated at discretion of the treating radiation oncologist, usually the largest lesion
3. IMRT per protocol
4. Physical examination, BPI, EORTC QLQC30

2.0 Background: Bone and Spinal Metastases

Metastatic disease to the bone is a major source of morbidity for patients living with cancer. It is estimated that approximately 85% patients with breast, lung, and prostate cancer will develop bone metastases in their lifetime.(4) Other solid tumor malignancies including renal cell carcinoma, thyroid cancer, colorectal cancer, myeloma, and lymphoma have also been implicated in the development of bone metastasis. Overall, 40% of all bone metastasis will occur within the spinal column, with 5-10% of people developing symptomatic spinal cord compression. (11). The most common site involved is the lumbar spine. (1, 14) Untreated, the natural history of an asymptomatic spinal metastasis is a progressive development of localized pain, compression fracture, spinal cord compression, or a combination and the associated comorbidities that follow.

Traditionally, treatment of spinal metastases has been considered palliative and is given to reduce symptoms of disease progression. The overall prognosis for patients with bone metastases remains poor, with the median survival most closely related to the primary tumor histology, performance status, and presence of concurrent visceral metastases. For some patients such as those suffering from bone-only metastatic breast or prostate cancer, life expectancies can be in excess of 2 to 4 years.(4, 18) Nowadays with improved surgical and radiotherapy techniques, as well as targeted systemic therapy, cancer has become more of a chronic disease than a terminal illness. Arguably, eradicating bone metastases before debilitating symptoms develop could provide better quality of life independent of a patient's life expectancy.

2.1 Current Standard of Care

Surgery, radiation, and chemotherapy each play a role in the treatment of metastatic spinal disease; however, conventional radiation has historically been the mainstay of treatment. Spinal metastases are generally treated once symptoms develop (primarily pain), and are addressed palliatively with the intent of symptomatic control. Current standard of care uses broad radiation portals which encompass the involved vertebral body level(s), with a margin of normal tissue measuring at least 2cm in all directions. (RTOG 97-14). Clinically, this can equate to including one normal vertebral body level superiorly and inferiorly, and approximately 2cm lateral to the transverse

processes. Fractionation schemes vary, but the most commonly used regimens are 4000 cGy in 200cGy fractions and 300cGy in 300cGy fractions. Different fractionation schemes have been compared extensively in several different trials, with the end result being relatively equivalent results in time to pain relief, proportion of partial and complete pain improvement, but where they differ is primarily in the duration of symptomatic control, with longer control seen with the use of more protracted treatment courses. Documented rates of partial pain improvement are in the range of 70-90%,(9) and complete pain relief in approximately 40-50% of patients.

In a retrospective review of 1,304 patients, Rades et al. found in-field recurrences of tumor at 2 yrs for different fractionation schemes to be: 24%(1x8Gy), 26%(5x4Gy), 14%(10x3Gy), 9%(15x2.5Gy), and 7%(20x2Gy), (p=<.001). (14) This is one of the few studies that has separated in-field recurrence from symptomatic recurrence, for which multiple studies including the RTOG 97-14 short versus long course comparison study have published re-treatment rates for palliation of symptoms in up to 25% for single fraction and 7-10% for fractionated regimens. (9,10,11)

It is apparent that there are many different fractionation regimens used for treatment in radiation oncology. The concept of biologically equivalent dose (BED) based on observed cell killing in vitro, was developed in an attempt to allow radiation oncologists to approximate the effects of differing dose fractionation schemes on acute and late reacting tissues. The mathematical description of this concept is BED = nd (1+d/(α/β)), where n= the number of fractions of radiation given, d=the dose/fraction in Gy and the experimentally determined factor α/β described killing for different types of tissues. Late responding tissues such as spinal cord are considered to have an α/β of 2 in contrast to acute responding tissues such as tumor or bone marrow which have been estimated to have an α/β value of approximately 10. In assessing damage to normal tissues, Emami et al originally described the radiation tolerance, described as the Toxic Dose (TD) 5/5 (the dose associated with the development of tissue toxicity in 5% of patients at 5 years) of the spinal cord to be 45-50 Gy delivered in 180-200cGy fractions to 5cm length (from above equation with fraction size 2Gy = 90Gy BED_2) (5). Each tissue has a defined endpoint such as transverse myelitis in spinal cord. More recent studies have suggested that the true tolerance of the spinal cord to fractionated radiation

(180-200cGy) is in the range of 63-70 Gy (18). Regardless, considering the current treatment schemes for palliation of spinal metastases using 3000 cGy in 10 fractions (BED_2 75 Gy) or 800 cGy in 1 fraction (BED_2 40 Gy), the accepted tolerance of the spinal cord is met with a single treatment course. Exceeding spinal cord tolerance places a patient at risk for transient or chronic progressive myelopathy. If spinal cord tolerance is met with a single treatment course, there are not many options for retreatment should the patient have progression, which from RTOG 97-14 showed us can happen in up to 25% of cases.

Retreatment of the spinal cord using conventional techniques can be done with acceptable results, and sufficient data supports this technique. Still, long term data clearly documenting the true tolerance of the spinal cord is lacking. One of the current areas of increased interest is to use stereotactic body radiation therapy to retreat recurrent spinal metastatic disease by effectively avoiding significant dose to the spinal cord as much as technically feasible. (17)

2.2 High Dose Conformal Radiation Therapy

Intensity Modulated Radiation Therapy (IMRT) is a form of radiation therapy treatment delivery whereby a radiation treatment is generated in an "inverse planning" method. After a patient has undergone a CT simulation procedure, particular structures called organs at risk (OAR), such as the parotid glands in the treatment of Head and Neck cancers, can be contoured on the treatment planning system. Maximum dose limits can be set for the OARs based on this 3-dimensional contour, and a treatment plan is generated that delivers the necessary curative dose of radiation to the tumor, while at the same time sparing normal tissues the parotid glands based upon the limits set earlier. A typical IMRT treatment plan will utilize 5, 7, or 9 beams in an effort to gain coverage on a tumor and spare OARs. In contrast, conventional radiation therapy uses fewer beams, and utilizes "forward planning." A treatment plan is generated with the goals of adequate dose coverage to the tumor, with OARs receiving whatever dose of radiation they may receive; normal tissue sparing is more difficult to achieve using conventional approaches.

One of the principle advantages behind IMRT is its inherent ability to escalate the dose of radiation to levels much higher than would be permissible with conventional techniques, while at the same time limiting the dose of radiation to OARs. By definition, Stereotactic Body Radiation Therapy (SBRT) refers to the treatment of an isolated cancer in 2-5 fractions. Often, SBRT can be optimized by the use of IMRT to deliver high doses of radiation in a few fractions and utilizes patient immobilization to reduce set-up error and patient movement; in contrast to conventional radiation techniques, which delivers smaller doses in multiple fractions. Combining the improved conformality of the radiation dose distribution using IMRT, and the immobilization of the patient is the only safe method for dose escalation and the relative sparing of normal tissues. This has well described as both a safe and effective treatment modality for multiple sites of localized disease and most recently trials have begun to evaluate its utility in the treatment of the spine.

One of the main advantages of IMRT in the treatment of spinal metastases is the ability to sharply delineate dose distributions and spare adjacent structures. Ryu et al. and Yamada et al. demonstrated that by using a margin of 5mm between the treatment volume and the structure of interest (ie the spinal cord), high dose SBRT delivered using IMRT can be given safely with single fraction disease of up to 18 Gy (BED = 180Gy, $\alpha/\beta=2$) without significant toxicity. (16, 20, 21). In a recent study in female Yucatan pigs (considered a good human analog), Medin et al (unpublished) showed not only recovery of cord tolerance over a 3 year period to pre-irradiation tolerance but that re-irradiation with a 16 Gy single fraction irradiation produced no toxicity. Additionally, in contrast to full circumferential irradiation of cord, partial thickness cord irradiation has higher dose tolerance in experiments in progress.

2.3 Radiation Prescription Dose

In a review of the linear quadratic model of cell killing by radiation, it is apparent that large fractions of radiation kill cells on the "linear" portion of the curve and by definition are very effective especially in being less influenced by factors such as hypoxia or cell cycle. The difficulty with large fractions (>600-800cGy) is maintaining normal tissue toxicity to an acceptable level. As a palliative modality, considerations of

fractionation include the symptoms to be palliated ("oncologic control") vs. toxicity to normal tissues. Ideally, one would like to achieve high local control with low toxicity with a radiation regimen delivered in the shortest possible time.

Improved local control rates in brain, lung, liver, and pancreas cancers have been seen with the use of high dose, single fraction IMRT. Prostate, lung, and breast tumors are responsible for up to 90% of bone metastases. Multiple dose escalation studies have been carried out for these sites demonstrating that higher tumor doses equate to improved cell killing. Onishi et al. in a Japanese trial of hypo-fractionated high dose radiation for primary lung cancers, demonstrated an improved 5yr Progression Free Survival (PFS) and Overall Survival (OS) for patients who received a BED_{10}>100Gy. (13) Similarly, the MRC Prostate trials comparing 64Gy vs 74Gy, the Dutch Prostate trials comparing 68Gy vs 78Gy, and MD Anderson trials comparing 70Gy vs 79Gy have all shown improved disease free survivals on long term follow-up with higher doses of radiation. Comparing radiation doses to an intact primary tumor compared to a metastatic bone lesion, it is not surprising that the RTOG documents recurrence rates and the need for retreatment in up to 10% and 25% of cases treated palliatively.

Ideally, if enough of the spinal cord can be spared from the radiation dose, higher effective doses could be directed to the site of disease that would both palliate symptoms and eradicate tumor. Gertzen et al. treated 393 patients with 500 verified symptomatic spinal metastases (excluding neurologic deficits or spinal cord compression) using single fractionated SBRT with doses of 12.5 to 25 Gy (BED 90.625 Gy and 337.5 Gy respectively), and found response rates of pain improvement in 86% and long-term tumor control of 88% at median follow-up of 21 months. Local control rates of 90% at median follow-up of 15 months were also found by Yamada et al. (20) in a series of 93 previously irradiated patients, now treated for recurrence at Memorial Slone Kettering with single fraction radiotherapy using doses of 18-24 Gy.

For the majority of cases of toxicity that have occurred using single fraction high dose radiation to treat spinal lesions, these occurred during dose escalation studies or were attributed to extenuating patient circumstances that were likely contributory. However, apparently safe limits have been published by Ryu et al. (16) who described the treatment of recurrent spinal metastases in patients previously treated with conventional

radiation therapy. This trial has established a minimum partial tissue tolerance of the spinal cord to hypofractionated radiation therapy of 10Gy to 10% volume defined by involved area of disease plus a 6mm craniocaudal margin. In this study, there was a statistically significant difference in pain symptoms for doses in excess of 14 Gy. Additional data suggests that the spinal cord can tolerate a maximum point dose of 13-14 Gy in a single fraction. (6-8) Multiple studies have demonstrated that single fraction high dose radiation to the spine can be administered safely with a complication rate of <1%. (17, 20). No cases of spinal cord injury were documented in the series from Germany published by Gertzen. (6-8) Yamada et al. also demonstrated no cases of radiculopathy or myelopathy, although grade 1/2 esophagitis and skin toxicity were observed in 3 patients, and acute compression fracture occurred in 3 patients. (20) In the study by Ryu et al, one patient developed radiation-induced cord injury 13 months following treatment of single fraction RT of dose 16Gy, with max point dose 14.2Gy, and dose to 10% volume 9.6Gy. The patient incidentally was treated with additional chemotherapy with Carboplatin/Taxol. After administration of steroids, the patient had a complete symptomatic resolution. Overall, high dose single fraction radiation to the spine appears to be safe when dose restraints to the spinal cord are met.

In summary, there is accumulating data to support the concept that a single fraction RT using IMRT to deliver a minimum conformal dose of 14Gy (BED = 116Gy, $\alpha/\beta=2$) can palliate symptoms of vertebral spinal metastases, control disease locally, and maintain low radiation doses to spinal cord that would not preclude a patient from receiving additional therapy in the future.

2.4 Health Related Quality of Life and Utilities

Skeletal related events (SREs), defined in this study as a pain attributable to bone metastasis, pathological bone fracture, spinal cord compression, surgery to bone, or radiation to bone, have important and significant effects on measures of health-related quality of life.

2.4.1 The Brief Pain Inventory (BPI)

The BPI, developed by Daut et al., was modeled after the McGill Pain Questionnaire. The BPI is a seventeen-item patient self rating scale assessing demographic data, use of medications, as well as sensory, and reactive components of pain. Respectable reliability has been demonstrated over short intervals using test retest item correlation; worst pain, ($r = 0.93$); usual pain, ($r = 0.78$); and pain now, ($r = 0.59$). Evidence of validity of the BPI comes from several sources. The relationship between use of pain medications and overall pain ratings was examined. The percentage of patients taking pain medications increased with high pain ratings. Significance was demonstrated between increased medication use and high pain ratings for bother narcotic ($x = 28.17$, $df = 3$, $p < 0.002$) and non-narcotic ($x = 23.75$, $df = 3$, $p < 0.002$) for pain relievers. Validity of the BPI was also supported by the moderate correlation between worst pain intensity ratings and ratings of interference with six areas of activity and mood ($r = 0.245$ to 0.478, $p < 0.02$ for all but social relationships were $p < 0.05$). And finally, there is a logical pattern in the differences in inter-correlations among various pain and activity interference measures for different diseases.

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 including depression, suffering, and perceived availability of relief. The BPI's ease of translation (validated in 12 languages) and brief administration have made it a frequently used tool in clinical trials in which reduction or prevention of pain are primary or secondary outcome measures, and it is considered the FDA standard for a pain assessment tool.

2.4.2 EORTC Quality of Life Questionnaire (QLQ-C30)

In 1986, the EORTC initiated a research program to develop an integrated, modular approach for evaluating the QoL of patients participating in international cancer clinical trials. This research resulted in the development of a core questionnaire which is referred to as the EORTC QLQ-C30 (Aaronson et al., 1993). The EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (Physical, Role, Cognitive,

Emotional, and Social Functioning); three symptom scales (Fatigue, Pain, and Nausea/Vomiting); and Global Health Status/QoL scale. Six single item scales are also included (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties). The psychometric properties of the questionnaire were tested and in conclusion it was found to possess the required standards such as validity (measuring what it is intended to measure), reliability (measuring with sufficient precision), and sensitivity (ability to detect changes) (Aaronson et al,. 1993; Osoba et al., 1994; Kaasa et al., 1995). The questionnaire was initially tested in a population of lung cancer patients (Aaronson et al., 1993) and subsequently in a variety of cancer patient groups. A bibliography is contained in the EORTC QLQ-C30 Scoring Manual (Fayers et al., 2001).

There is a continuing program of development for the EORTC QLQ-C30. There have been four versions of the questionnaire: the QLQ-C30 version 1.0, the interim version QLQ-C30 (+3), which introduced new questions for the Role Functioning and Global Health Status/QoL scales, the QLQ-C30 version 2.0, which was released after validation of the new questions, and the current version 3.0 of the QLQ-C30. Version 3.0 differs from version 2.0 only in that it has four-point scales for the first five items comprising the physical functioning scale. Data from all four versions are used in this manual, but only the current versions of the Global Health Status/QoL, Physical Functioning and Role Functioning scales are reported: this means that available sample sizes for these three scales will generally be lower. In previous publications the abbreviations QL2, RF2, and PF2 are often used to distinguish the revised versions of these scales from the original versions but in this manual QL, RF, and PF will instead be used to denote the current versions. The remaining 12 scales have remained unchanged throughout the history of the questionnaire.

2.5 Hypothesis

Given the high rates of vertebral metastasis from many cancers, the primary objective of the study is that up front treatment of metastatic lesions will alter the time to progression and development of associated symptoms.

3.0 Objectives

Primary

1. Time to any skeletal related event most commonly symptomatic recurrence or progression with pain/neurologic impairment with evidence of radiographic progression.

Secondary

2. Safety and toxicity. Patients will be monitored for minimum of one year for both acute and late effects including non-malignant compression fracture, progression of pain, and Quality of Life.

4.0 Eligibility

1. Histological confirmation of malignancy (non-small cell lung cancer, breast cancer (hormone refractory), prostate cancer (hormone refractory), lymphoma, renal cell carcinoma, myeloma by either biopsy or cytology of the primary or metastatic lesion.
2. Patients must have radiological documentation of metastatic disease to the thoracic or lumbar spine which may include computer assisted tomography (CAT scan), positron emitted tomography (PET) or nuclear medicine bone scan (NMBS). Magnetic resonance imaging (MRI) is required prior to treatment planning to confirm the extent of the disease and is used for defining the target for the radiation.
3. Patient with ≥1 asymptomatic spinal metastases of the thoracic spine OR ≥1 asymptomatic spinal metastases of the lumbar spine may be included. Patients with spinal metastases to multiple vertebral levels may be included at the discretion of the investigator; however, only one vertebral level will be treated.
4. Spinal metastatic lesion being treated must be ≤ 6cm in greatest dimension.
5. Tumor to be treated should not directly abut the spinal cord, and should have at least 5mm separation from the spinal cord. For patients with tumors closer than 5mm, inclusion is permissible at the discretion of the treating radiation oncologist such that dosimetric review demonstrates that the total dose to spinal cord is within tolerable range of <10Gy to 10% partial volume or max point dose 18 Gy.

6. Patients must be able to fit into either the Civco stereotactic immobilization or the Elekta Stereotactic BodyFix immobilization device.
7. Must be ≥ 18 years of age.
8. ECOG status 0-2.
8. Women of childbearing potential and male participants must use an effective contraception method. (Until at least 60 days following treatment.)
9. Negative urine pregnancy test within one week before starting treatment in women of child-bearing potential.
10. Patients must sign a study-specific informed consent form.

4.1 Exclusion Criteria

1. Patients with evidence of spinal instability OR neurologic deficit resulting from bony compression of neurologic structures.
2. Patients with other systemic illness, or have not recovered adequately from their primary treatment or who have evidence of progression of their current cancer prior to therapy that, in the investigator's opinion, would preclude their inclusion.
3. Patient may not receive concomitant cytotoxic anti-neoplastic therapy during treatment. Patients may be allowed to use hormonal suppression therapy or bisphosphonates for hypercalcemia.
4. Pregnant or lactating women.
5. Any patient with symptoms of pain, compression fracture, neurologic deficit attributable to spinal metastases will not be included.
6. Patients previously treated with radiation therapy to the thoracic or lumbar spinal levels of involved disease will not be included.

5.0 Pretreatment Evaluations

(All lab tests and radiographic studies should be obtained within 4 weeks of study entry)

5.0.1 Complete history, physical examination, and evaluation of Zubrod Performance Status.

5.0.2 Pathological (biopsy) or cytologically proven malignancy

5.0.3 NMBS, CT, or PET and MRI demonstrating findings consistent with metastatic disease.

5.1 Schema

Patients will be accrued and distributed into one of two strata:

1. Patients with a single confirmed spinal metastasis within the thoracic or lumbar spinal levels. These patients will be treated to the single metastatic lesion.

2. Patients with ≥2 confirmed spinal metastases within the thoracic or lumbar spinal levels. These patients will have a single lesion selected at the discretion of the treating radiation oncologist for treatment, usually the largest lesion while respecting dosimetric limits. The remainder of the spinal metastases will serve as internal controls, and further treatment will be withheld unless symptoms of progression are identified.

6.0 Treatment Plan

All radiation therapy must be planned and delivered with IMRT-based delivery system. Non-contrast CT images will be obtained in 2.5mm slices, and fused with the patients pre-study entry MRI T2 or 1 weighted images depending on the method yielding best resolution of the tumor upon fusion with the treatment planning CT scan. Tomotherapy is allowed.

6.1 Volume and ICRU Point Definitions

The definitions of volumes are in accordance with the 1993 ICRU Report#50:45 Prescribing, Recording and Reporting Photon Beam Therapy. At the time of CT simulation, the patient's most recent MRI T1 weighted post-contrast axial images will be fused with the non-contrast CT simulation films.

6.1.1 Gross Tumor Volume (GTV) is defined by the physician as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary tumor as defined on planning CT corresponding to the contrast-enhancing area on MRI T1 weighted images.

6.1.2 Clinical Target Volume (CTV) will have no additional margin for microscopic extension and will be the same as the GTV.

6.1.3 Planning Target Volume (PTV) is defined by the physician as known gross disease as defined by planning CT expanded to include the entire vertebral body and pedicles. When there is a paraspinal or epidural component, the involved spine and the gross visible tumor will be included in the target volume.

6.1.4 The ICRU Reference Point is to be located in the central part of the PTV. Typically, this point should be located on the beam axis or at the intersection of the beam axes (isocenter).

6.2 3-D Planning

6.2.1 Planning Volume: The PTV is to be treated with any combination of coplanar or noncoplanar 3-dimensional beams optimized with IMRT or with tomotherapy-based IMRT shaped to deliver the specified dose while restricting the dose to the normal tissues.

6.2.2 Dose Specification:

Field arrangements will be devised under the discretion of the treating physician, and all patients will be treated at 14-16 Gy single fraction dosing using 6MV photons. While it is expected that single fraction of high dose radiation will be delivered, for difficult geometry the treatments may be fractionated to up to 3 fractions providing critical organ tolerances are maintained. All attempts are to be made to cover the contoured GTV by a minimum of 95% prescribed dose.

6.2.3 All patients will have 3-Dimensional CT Planning with attention to dose limiting organs. Complete dose volume histograms must be provided and include (at a minimum) spinal cord, heart (where applicable), lung (where applicable), and esophagus (where applicable), gross tumor volume (contoured gross disease), planning target volume (involved vertebral body(s) and spinal cord).

6.3 Normal Tissue Volume and Tolerances

6.3.1 Efforts will be made to maintain dose limits as described below, and total dose received by partial volumes of 5%, 15%, 25%, and 50% will also be recorded for further dose tolerance evaluation. The treating radiation oncologist will assess the treatment

parameters to ensure dose-limiting organs remain within the commonly accepted levels considered relatively safe. It is expected that most patients will be treated with Tomotherapy. This technology uses arc-based IMRT to deliver rotational therapy to the PTV. Dose limitations will be defined in the IMRT-based plan as per Table 6.3.1 taking into account any previous radiation delivered. In a static IMRT plan using a minimum of 7 beams, each will contributing only approximately 200cGy of the total prescribed dose of 14-16 Gy. If any beam traverses a critical organ, the dose delivered will be considered and a maximum point dose to any organ considered as well. Table 6.3.1 lists common maximum dose limits to a point or volume within several critical organs to be considered when stereotactic radiotherapy is used. Size of fraction delivered to each organ during each conformal treatment must be considered, since not all beams will either enter or exit through a structure. All attempts will be made to keep entrance and exit doses of each fraction traversing a critical organ to as close to a maximum of 200 cGy as possible to help estimate critical structure doses. All critical organs will be contoured and doses calculated in a standard fashion. Composite plans incorporating the initial radiotherapy and the high dose IMRT plan must be created to accurately assess tolerances.

Table 6.3.1

Serial Tissue	Volume	Volume Max (Gv)	Endpoint(Grade 3)
Spinal Cord	Less than or equal to 0.35cc	10 Gy	myelitis
AND			
Spinal Cord	Less than or equal to 10% of the partial spinal cord	10 Gy	myelitis
AND			
Spinal Cord	Less than or equal to 0.03cc	14 Gy	myelitis
Cauda Equina	<0.03 cc <5 cc	16 Gy 14 Gy	neuritis
Sacral Plexus	<0.03 cc <5 cc	18 Gy 14.4 Gy	neuropathy
Esophagus*	<0.03 cc <5 cc	16 Gy 11.9 Gy	stenosis/fistula
Ipsilateral Brachial Plexus	<0.03 cc <3 cc	17.5 Gy 14 Gy	neuropathy
Heart/Pericardium	<0.03 cc <15 cc	22 Gy 16 Gy	pericarditis
Great vessels*	<0.03 cc <10 cc	37 Gy 31 Gy	aneurysm

Trachea* and Larynx	<0.03 cc <4cc	20.2 Gy 10.5 Gy	stenosis/fistula
Skin	<0.03 cc <10 cc	26 Gy 23 Gy	ulceration
Stomach	<0.03 cc <10 cc	16 Gy 11.2 Gy	ulceration/fistula
Duodenum*	<0.03 cc <5 cc	16 Gy 11.2 Gy	ulceration
Jejunum/Ileum*	<0.03 cc <5 cc	. 15.4 Gy 11.9 Gy	enteritis/obstruction
Colon*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	colitis/fistula
Rectum*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	proctitis/fistula
Renal hilum/vascular trunk	<2/3 volume	10.6 Gy	malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gv)**	**Endpoint (Grade 3)**
Lung (Right & Left)	1000 cc	7.4 Gy	Pneumonitis
Renal cortex (Right & Left)	200 cc	8.4 Gy	Basic renal function

7.0 Stereotactic Dose Specifications

7.1.1 Stereotactic Targeting and Treatment

Civco Stereotactic positioning system or Elekta Body Fix System will be used for patient setup.

7.1.2 Patient Positioning

The patient's position must be accurately reproducible from treatment to treatment in the supine position. Within the immobilization system, the patient will be positioned on Vac-loc pillows to conform to patient's external contours.

7.1.3 Inhibition of Effects of Internal Organ Motion

Abdominal compression to the maximum as tolerated by the patient will be used to minimize the effect of internal organ motion at the discretion of the treating physician. Ideally, compression will produce damping of the diaphragmatic movement to 0.5-1.0 cm as determined by fluoroscopy (conventional) or alternatively by the creation of maximum intensity projection (MIP) CT images to determine respiratory excursion of the target vertebral body.

7.1.4 Localization

Immediately before each treatment, mV (Tomotherapy) or kV cone beam CT (conventional linac) isocentre localization will be done on the treatment unit to ensure proper accurate targeting of the tumor volume.

7.2 Treatment Planning/Target Volumes

7.2.1 Image Acquisition

Treatment planning will utilize computed tomography (CT). The planning CT will be obtained with the patient in the body frame to allow simultaneous view of the patient's anatomy and fiducial system. 3mm thick axial slices will be obtained with the gantry angle at 0 degrees. The CT images will be fused with the patient's pre-treatment T1 Weighted Post contrast axial images by an appropriately trained Dosimetrist. Contouring of the GTV will be accomplished using CT Bone windowing or soft tissue windows with contrast, with verification of the fused T1 MRI images. Only abnormal density on CT consistent with gross tumor will be included in the GTV. No margin or enlargement will be permitted for presumed microscopic extension (ie GTV = CTV). The PTV will include an expansion of the GTV to include the remainder of the vertebral body(s) involved, with greatest diameter dimension not to exceed 6cm.

7.2.2 Dosimetry

Each case will have Tomotherapy or conventional IMRT arrangements designed to deliver highly conformal prescription dose distributions per the UK institutional standard. The isocenter will be defined as the common point of gantry and couch rotation for the treatment unit. The isocenter in stereotactic coordinates will be determined from system fiducials and translated to the treatment record. The field aperture size and shape will correspond nearly identically to the projection of the PTV along a beam's eye view, except when observing the minimum field dimension of 3.5cm in the treatment of small lesions. Hotspots will be manipulated to occur within the target and not within adjacent normal tissue.

7.2.3 Dose Fractionation

The prescription dose of 14-16 Gy for a single fraction or 8Gy for three fractions (24 Gy total) will be delivered to the margin of the PTV covering a minimum of 95% of the PTV. Three fractions will be used in cases where the GTV is in close proximity to the spinal cord such that fractionation will provide improved spinal cord sparing at the discretion of the treating radiation oncologist. Planning will include correction for dose inhomogeneity (e.g. air, bone)

7.3 Technical Factors

7.3.1 Physical Factors

Treatment will consist of photon (x-ray) beams produced by a linear accelerator including Tomotherapy. 6MV energies will be used under most circumstances, with energies of 15-18MV used only in a limited number of beams (maximum 2) that must travel a cumulative distance of more than 10cm through soft tissue (not lung) to reach the isocenter.

7.3.2 Minimum Field Aperture

A minimum field dimension of 3.5cm is required for any field used from treatment delivery. If the minimum fields exceeds the technical requirements for small lesions (<2.5cm axial GTV dimensions or <1.5cm cranio-caudal GTV dimensions), the prescription dose is still prescribed to the edge of the defined PTV.

8.0 Patient Assessments

Assessments	Pre-Study Entry	1mo (+/- 3days) Post SBRT	3mo (+/- 7days) Post SBRT	Follow-Up[a,b]
History/Physical	X	X	X	X
Pregnancy test[c]	X			
MRI of T/L Spine	X			X[d]
Full body PET, CT spine and/or NMBS	X			X[d]
Pathology Review	X			
Toxicity Eval		X	X	X
BPI & EORTC QOL Evals	X	X	X	X

a: Follow-up intervals as per institutional standards (recommended approximately q3month).
b: Follow-up period of 1 year.
c: As indicated.
d: As clinically indicated

8.1 Baseline Documentation of Metastatic Lesions

Patient will be required to have imaging of the thoracic or lumbar spine including PET, CT and/or NMBC prior to study enrollment. In addition, MRI corresponding to the areas of involvement must be obtained prior to treatment planning. Attempts will be made to quantify maximum tumor dimensions based upon the largest diameter (LD) measurable on pre-treatment MRI images. This will be reported as the baseline LD, and will be used if applicable, for comparison in order to document radiographic disease progression.

9.0 Criteria for Evaluation

The endpoints for this study are to determine time to symptomatic recurrence in asymptomatic patients. In other words, we will assess the levels of pain perceived by the patients and overall quality of life as follows:

9.1 Brief Pain Inventory

This scale was developed in 1983 and has been validated in multiple national clinical trials. It is intended to obtain estimates of pain prevalence and severity. Ratings are on a scale of 0-10. It is a 10 item scale evaluating:

1. Demographic data
2. Use of Medication

3. Components of Sensory pain:

- Severity
- Chronicity
- Location
- Degree of relief relative to therapy

4. Reactive components of pain:

- Depression
- Suffering
- Perceived availability of relief

9.2 EORTC QLQ-C30

Developed by the EORTC Quality of life study group and consists of 9 multi-item scales measuring:

- 5 functional scales (physical, emotional, role, cognitive and social)
- Global QOL
- 3 symptom scales (fatigue, pain, nausea and vomiting)

It has been validated in over 2200 registered studies.

9.3 Symptom Development

Patients will be followed as per schema for one year. The first symptoms of tumor recurrence are expected pain and/or neurological changes localizable to the treated area. If symptoms are noted, an MRI or PET scan will be done as per standard of care.

9.4 Radiographic Response Criteria

9.4.1 Evaluation of Metastatic Lesions

Patients will undergo repeat imaging as clinically indicated. For patients in whom disease progression or recurrence is suspected, additional imaging in the form of CT scan or MRI may be obtained. An attempt to define extent of disease progression/recurrence can include, but is not limited to, comparison of maximum tumor diameter with pre-treatment imaging; evaluation for abnormal NMBS tracer uptake; evaluation for pathological enhancement of CT/MRI contrast material; or other radiographic documentation of progression.

9.5 Definition of Local Failure

Refers to the primary treated tumor after protocol treatment and corresponds to meeting the following criteria:

1. Evidence of symptomatic tumor progression (ie pain, compression fracture, or neurologic deficits such that radiation toxicity cannot be attributed).

AND

2. Radiographic evidence of disease progression/recurrence with corresponding activity on PET/CT or NMBS, or contrast enhancement on MRI.

10.0 Statistical Considerations

10.1 Sample size and power.

The primary endpoint of this study is to determine the feasibility of using stereotactic radiotherapy for treatment of asymptomatic spinal metastases to decrease the recurrence rate of pain/neurologic impairment and/or radiologic recurrence/progression within a 24 month follow-up period. Our hypothesis is that without treatment, approximately 75% or more of these patients will become symptomatic from their spinal metastasis within one year from identification. With treatment, there is sufficient literature to suggest a local control rate of 80-100%. As a feasibility study, we propose to enroll 26 patients evaluable-for-outcome, equally divided between the two strata. In comparison to literature-derived data, this will provide 80% power to detect a null hypothesis rate of 60% or higher versus an alternative (treated) rate of 35% or less. This equates to being able to detect at least a 42% reduction in progression, or local control rate of those patients whom we would expect to progress to symptoms.

We anticipate that progression rates may very well differ with respect to cancer site (eg. lung vs prostate). With our enrollment of 26 patients total, we anticipate obtaining at least 5 non-small cell lung cancer patients, at least 5 prostate (hormone refractory) cancer patients, and 5 breast (hormone refractory) cancer patients. Within each of these sub-groups, we have precisely 83.5% power to detect a null hypothesis rate of 75% or greater versus an alternative (treated) rate of 15% or lower, which equates to being able to detect an 80% or greater reduction in progression.

10.2 Analysis

NCSS PASS was used to perform the aforementioned power calculations. A one-sided binomial hypothesis test with a target significance level of 0.05 was employed to assess power and sample size and will be used to assess the rate of progression for the 26 enrolled patients as well as sub-groups where the sample size is larger than 5.

11.0 Reporting Toxicity

All patients will be assessable for toxicity, and those with measurable disease will be assessable for response. All grade 4 or grade 5 toxicities that are attributable to radiation therapy will be reported to the DSMB and Institutional Review Board within 24 hours of discovery. The stereotactic radiotherapy will be given in a one, or three day prescription with a minimum 40 hours between doses. Definitions of acute versus late effects will be used as below. Monitoring of late effects (most notably for Chronic Progressive Myelopathy) of radiation therapy will continue for the duration of the 12 month follow-up period.

11.1 Acute Radiation Toxicity: Acute (≤ 90 days from RT start) side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov)

11.2 Late Radiation Toxicity: Late (> 90 days from RT start) side effects will be documented using the NCI Common Toxicity Criteria version 3.0

11.3 Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment, will be reported directly to the DSMB and IRB.

12.0 Data and Safety Monitoring Plan

DSM committee will meet every 6 months to review patient safety and toxicity reports.

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