PROTOCOL DATE: 2015-JUL-24
CCTG TRIAL: SC.24

AMENDMENT #1: 2017-FEB-02
AMENDMENT #2: 2018-APR-03

AMENDMENT #3: 2018-OCT-31

CANADIAN CANCER TRIALS GROUP (CCTG)

A RANDOMIZED PHASE II/III STUDY COMPARING STEREOTACTIC BODY RADIOTHERAPY (SBRT) VERSUS CONVENTIONAL PALLIATIVE RADIOTHERAPY (CRT) FOR PATIENTS WITH SPINAL METASTASES

CCTG Protocol Number: **SC.24**

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to CCTG.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to CCTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified Investigator
(printed name and signature)

Date

Protocol Number: CCTG SC.24

CENTRE: _____

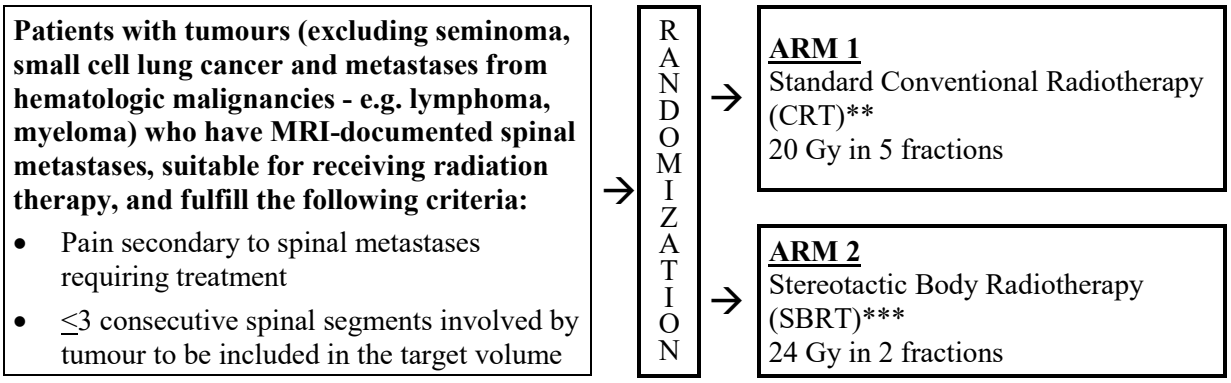
TREATMENT SCHEMA

This is a randomized, non-blinded multicentre phase II/III study in patients with spinal metastases.

Stratification

1. Histology (radioresistant♦ vs. radiosensitive♦)
2. "Mass"* on imaging (present vs. absent)
3. Centre

♦ radioresistant are renal cell carcinoma, melanoma, sarcoma and gastro-intestinal; radiosensitive are all other types
* refers to tumour that involves the paraspinal tissues or presence of epidural disease (extra osseous disease extension)



** Standard Conventional Radiotherapy will be referred to as "CRT" throughout this protocol.

*** Stereotactic Body Radiotherapy will be referred to as "SBRT" throughout this protocol.

Primary Endpoint - Phase II

The ability to accrue 54 patients over a 18 month period to a study that randomizes patients with spinal metastases to Stereotactic Body Radiotherapy (SBRT) or Standard Conventional Radiotherapy (CRT) within a Canadian multicentre setting.

Primary Endpoint - Phase III

The primary objective of the phase III study is to assess complete pain response in the treatment area at 3 months post-radiation.

Secondary Endpoints

- Complete pain response in the treatment area at 6 months post-radiation
- Radiation site progression-free survival (RSS PFS) at 3 and 6 months
- Spinal Instability Neoplastic Score at 3 and 6 months
- Overall Survival
- Adverse event profile
- Health–Related Quality of Life
- Economic Analysis
- Radiotherapy Quality Assurance (RTQA) compliance

Tertiary Endpoint

- Radiomics
- Biobanking for future correlative studies

1.0 OBJECTIVES

1.1 Primary Objective

Phase II Study

The primary objective of the phase II feasibility study is to assess the ability of Canadian investigators from multiple institutions to randomize 54 patients with spinal metastases to SBRT or CRT over an 18 month period.

Phase III Study

The primary objective of the phase III study is to assess complete pain response in the treatment area at 3 months post-radiation.

1.2 Secondary Objectives

To assess both treatment arms with respect to:

- Complete pain response in the treatment area at 6 months post-radiation, based on the International Bone Metastases Consensus Working Party Criteria.
- Radiation site progression-free survival (RSS PFS) at 3 and 6 months, using MRI imaging.
- Spinal instability as measured by the Spinal Instability Neoplastic Score at 3 and 6 months.
- Overall survival.
- Adverse event profile, using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0).
- Health–Related Quality of Life as measured by the EORTC QLQ-C30 and QLQ-BM22 instruments.
- Economic analysis as measured by the EuroQol EQ-5D-5L instrument.
- Radiotherapy Quality Assurance (RTQA) compliance, using prospectively-defined protocol-specified quality assurance measures.

1.3 Tertiary Objective

- Radiomics analysis of collected MR images to identify predictive and prognostic biomarkers.
- Biobanking for future correlative studies.

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Spinal Metastases

Spinal metastases occur in up to 40% of cancer patients. Given more than 177,000 cancer diagnoses in Canada per year, 53,000 people are expected to develop spinal metastases annually *[Canadian Cancer Statistics 2011]*. Patients with spine metastases experience escalating pain with disease progression leading to pathological fractures and spinal cord compression *[Rades 2007; Rades 2010]*. These complications cause tremendous suffering and compromise quality of life. Management has been traditionally limited to the use of low-dose "locally palliative" CRT aimed at initial and temporary symptom control, but not necessarily durable tumour and pain control *[Rades 2010; Zeng 2012]*. Although initial pain relief is expected following CRT, rates of complete pain relief (or "complete response") are quite poor; when using standardized pain relief endpoints/criteria, rates of complete response range from 0-20% at 3 months post-treatment *[Zeng 2012; Nguyen 2011; Chow 2007]*. Furthermore, image-based local control rates are disappointing for bulky tumours, and have been reported to be approximately 45% at one year *[Mizumoto 2011]*. As progressive spinal metastases can be devastating, including the potential for malignant epidural spinal cord compression leading to paralysis and requirements for emergency surgery and/or further RT, improved therapies are a high priority.

2.2 SBRT for Spinal Metastases

With innovative radiotherapy technology and modern imaging capabilities, it is now possible to change the treatment paradigm for patients with spinal metastases. Rather than treating with low dose CRT, SBRT technology can be applied to the spine and deliver 2-6 times the biologically equivalent dose as compared with CRT. Stereotactic body radiotherapy has been defined by the Canadian Association of Radiation Oncology (CARO) SBRT Task Force as *"The precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extra-cranial body target with doses at least biologically equivalent to a radical course when given over a protracted conventionally (1.8-3.0 Gy/fraction) fractionated schedule."[Sahgal 2011]* The intent of SBRT for spinal metastases is to safely deliver higher doses of radiotherapy, which will provide superior pain and local tumour control *[Sahgal 2008; Sahgal 2011]*. However, there is currently no evidence from randomized controlled trials or even high-quality multi-institutional cohort trials demonstrating that SBRT is superior to existing standards *[Sahgal 2008; Sahgal 2011]*. Furthermore, there may be potential for adverse events in the form of vertebral compression fracture which may be related to the SBRT as opposed to the natural history of the spinal metastases *[Sahgal 2013a]*.

Current evidence is limited to a few single-institution, single-arm, cohort studies reporting local control rates of ~80% *[Sahgal 2008; Sahgal 2011; Wang 2012; Al-Omair 2013; Thibault 2014]* and complete pain response rates of ~50% at 3 months *[Wang 2012; Nguyen 2009]*. These outcomes represent potential for major therapeutic gains to support the use of SBRT as opposed to CRT; however, at this time there are no high quality multi-centre clinical trial outcome data reported to understand the full implications of this treatment.

Despite the lack of high-quality evidence, spine SBRT is increasingly practiced in the United States, with ~60% of surveyed American radiation oncologists administering this treatment *[Pan 2011]*. In Canada, adoption of this technology has been more limited; only 6 of 41 radiation oncology centres currently provide spine SBRT*[Lund 2011]* with additional centres exploring its feasibility. Therefore, we are in the right environment to study spine SBRT in the form of a clinical trial.

2.3 Rationale for Current Study

The current standard of care in the management of patients with spinal metastases is to deliver CRT with palliative intent. Therapeutic goals are to preserve neurologic function and spine stability and to treat (and prevent) pain. For those with neurologic compromise or spinal instability, surgery followed by radiotherapy is a common treatment. The proposed trial does not address this population. Instead, we address the more common clinical problem associated with considerable patient suffering, in which spinal metastases cause debilitating pain. This clinical scenario may be a harbinger of neurologic compromise or spinal instability; radiotherapy, along with other standard components of palliative management, is the mainstay of management.

Successful radiotherapy is based on existence of a differential effect of radiation to induce death of tumour cells while avoiding injury to normal cells. These differential effects can result from intrinsic differences of tumour and host cell radiosensitivity and/or differential exposures of the tumour and host cells to radiation. Dose-response relations between radiation dose and tumour or host cell injury exist and can be predicted based on the dose of radiation exposure, referred to as the *biologically effective dose* (BED). A mechanism to maximize differential effects of radiation on the tumour while minimizing host cell injury is to ensure different BEDs are delivered to these respective tissues.

The radiobiologic rationale for SBRT is based on two principles. First, ultra-high doses per fraction administered in only a few fractions enhance tumour cell-kill by inducing greater tumour-cell death directly through apoptotic mechanisms, and indirectly through tumour vessel endothelial cell injury *[Balagamwala 2012; Garcia-Barros 2003]*. Second, with technologic advances, including computer software, modern CT and MR imaging can be directly fused with 3-dimensional radiotherapy planning and dose delivery. This capacity, coupled with new abilities to shape radiotherapy beams with use of *multileaf collimator* (MLC) systems located within the *linear accelerator* (linac) and the incorporation of image-guidance into the treatment process, mean that tumours can be precisely targeted with less normal tissue residing in the RT target volume, and lower BEDs directed at normal tissues immediately adjacent to the tumour *[Sahgal 2008; Sahgal 2011]*. As the potential benefit vs. harm of RT for patients with spinal metastases is determined by the differential BEDs that are directed at the tumour, as opposed to the adjacent spinal cord, these two principles of enhanced dosing to the tumour, including its administration in ultra-high doses per fraction, and sparing of normal tissue generate the hypothesis that SBRT will be a superior treatment and safe.

High dose-per-fraction stereotactic radiotherapy has been applied to treat for brain metastases since the 1980's *[Sahgal 2008b]*; initial testing in this clinical situation was made possible through abilities to immobilize the head using invasive surgical head frames. Five randomized controlled trials and a recent meta-analysis demonstrate that treating brain metastases with stereotactic radiotherapy is effective, safe and less neuro-toxic as compared with previous whole brain RT approaches *[Tsao 2011]*. As technologies became available to target body tumours with this same precision, and with the use of non-invasive body frames and modern linac delivery systems, a natural evolution was to apply these principles to body tumours and, hence, the genesis of SBRT. Initial development of SBRT involved testing in patients with lung cancer as a means to deliver ultra-high BEDs to improve local tumour control, given that outcomes with CRT were very poor. Based on outstanding results of a large phase 2 trial evaluating inoperable patients *[Timmerman 2010]*, SBRT has been adopted as a standard of care for these patients and 3-year local control rates of ~80% are seen *[Timmerman 2010; Taremi 2012]*; these rates are approximately double that expected with CRT and have promoted evaluation of SBRT as treatment for other cancers, including hepatocellular, prostate, pancreatic, and selected primary spinal tumours *[Lo 2010]*.

The developmental data associated with SBRT as treatment for patients with spinal metastases has been systematically evaluated. Available evidence consists of retrospective and prospective case series. The earliest review *[Sahgal 2008]* summarized the results of published series reporting the palliative and local control and benefits of SBRT in patients who had received no prior radiotherapy, were previously irradiated, were postoperative or were a mixed population. Only three studies provided data for complete pain relief; these ranged from 33 to 75%. These data are compromised by use of various measurement instruments and inconsistent durations of follow-up. Favourable rates of some degree of pain relief ranged from 67% to 100%. Crude local control data suggest excellent results, although with variable follow-up periods interpretations are limited. Local control was observed in 67/77 (87%) of those who had not previously received radiotherapy, 23/24 (96%) previously irradiated, 49/52 (94%) postoperative patients and in 568/655 (87%) of those included in reports assessing mixed populations. The technical, simulation and treatment details associated with SBRT development at the University of Toronto have been described *[Foote 2011, Hyde 2012]*. The initial treatment consisted of 24 Gy delivered in 3 fractions and preliminary results in a population predominantly pre-treated with radiation and chemotherapy yielded results consistent with published literature *[Massuci 2011]*. With greater experience, the dose-per-fraction was escalated and since 2011 treatment the standard of care at the University of Toronto has been 24 Gy in 2 fractions - the SBRT prescription for this randomized controlled feasibility study. Recent publications with this approach *[Al-Omair 2013; Thibault 2014]* have been reported by Sahgal's group showing consistent local control results and a risk of vertebral compression fracture that is clinically reasonable at ~10% *[Cunha 2012; Sahgal 2013a]*. This VCF rate is of significant importance as the use of the more aggressive single fraction dose of 24 Gy in 1, as advocated by some American Centers, has been shown to be associated with a 40% risk of VCF which is clinically unacceptable. This dose fractionation is also being increasingly adopted by the Japanese and UK radiation oncology community as their standard of care.

The importance of clearly establishing SBRT as superior treatment for patients with spinal metastases is evident when implications associated with its adoption are considered. For patients, technical processes of radiotherapy simulation and delivery are more arduous than with CRT. Treatment with SBRT requires that radiotherapy be delivered to the target with a precision of 1-2 mm. Very specific planning is thus performed, which includes simulation processes in which patients are immobilized for 30-60 minutes and may suffer from claustrophobia and incorporation of MR imaging into both treatment planning and follow-up. Balanced against these concerns is the potential for superior efficacy and a need to receive fewer treatment fractions. Thus, in addition to the need to clearly understand the efficacy benefits and adverse effect risks associated with SBRT, it is important to understand the patient experience associated with its administration.

For radiation oncologists, special training in SBRT is required. The recent CARO task force on SBRT advocated training in disease site-specific SBRT practices before treatment is undertaken, including through course work, mentorship programs or participation in clinical trials that include rigorous RTQA processes. Similar supports are required for the entire radiation oncology team, which includes radiation planners, physicists and technologists. For institutions and funders, adoption of SBRT may be associated with new capital expenditures and operational implications, including trade-offs associated with abilities to treat three or four patients with CRT in the time span required for SBRT. Clear understandings of efficacy, effectiveness and cost-effectiveness are needed to inform processes of health service planning.

Data from randomized phase II trial by Sprave et al (2018) evaluated the impact of SBRT (24Gy/1 fr to 3D CRT 30 Gy/10 fr) on pain relief as defined by a 2-point reduction of self reported pain, using a visual analogue scale and measured within the treated area at 3 months post radiotherapy. No significant difference was seen between treatment arms for pain relief at 3 months (p=0.13) but there was a trend towards greater complete pain response at 3 months favouring the experimental arm: 43.5 (SBRT) versus 17.4% (CRT) p=0.057. These results provide further justification for the conduct of the current study and inform the estimates for complete pain response in the CRT and SBRT arms (see Section 14.3).

We are aware of one other ongoing randomized controlled trial addressing this issue: the Radiation Therapy Oncology Group (RTOG) continues its slow accrual onto RTOG-0631 (NCT00922974), which compares CRT 8 Gy in 1 fraction with SBRT 16-18 Gy in 1 fraction. Investigators based within CCTG, including those who are international leaders in investigating the treatment of bone metastases have considered this protocol and concluded that two important limitations of this trial exist. First, the standard arm CRT is not considered a Canadian standard for patients with spine metastases and an expected survival or more than 3 months *[Chow 2007]*, as higher-dose fractionated treatment is preferred for those who are the primary candidates for SBRT. Second, we believe that the evolving experience with SBRT as treatment for spinal metastases suggests that higher doses given over 2 fractions as compared to one fraction will be more efficacious and safer.

In summary, the hypothesis that SBRT will provide palliation that is superior to CRT for patients with spinal metastases is based on a strong radiobiologic rationale, promising data associated with its adoption for other tumour sites, and highly suggestive developmental data obtained from prospective single-arm evaluations of treating patients with spinal metastases. However, there are important risks and incompletely understood implications associated with its premature adoption given the current absence of data from a randomized controlled trial.

As SBRT is complex and costly because it requires new technical resources, rigorous quality assurance, expertise in treatment planning, and adequate consent of patients regarding side effects, better evidence from a properly designed and conducted randomized controlled trial is needed before widespread adoption of spinal SBRT can be justified. Given universal patient access to provincially-organized Canadian cancer care delivery systems and as Canadian radiation oncologists have a strong investigative track record and are internationally recognized for their evaluation of radiotherapy practices for patients with bone metastases *[Zeng 2012; Chow 2007; Sahgal 2008; Sahgal 2011; Chow 2011; Chow 2002; Nguyen 2011; Sahgal 2009; Sahgal 2010]*, CCTG is well positioned to conduct such a randomized control trial.

Before embarking on a phase III trial, enabling data were needed to obtain information about the endpoints (timing, point estimates, standard deviations) and trial conduct compliance (accrual, Radiotherapy Quality Assurance [RTQA]).

We thus proposed to first conduct a randomized, non-blinded multicentre phase II feasibility study to obtain these enabling data and then embark on a phase III study should the essential trial metrics be supportive.

2.4 Health-Related Quality of Life

The main patient-reported outcome (PRO) of interest in this study is the secondary endpoint: worst pain scores analyzed according to the a-priori defined response categories of the International Bone Metastases Consensus Working Party Criteria. These assessments and analyses are described further in sections 10 and 14. In addition to pain scores, patients allocated to both treatment arms will complete the EORTC QLQ-C30 (core) and the QLQ-BM22 (bone metastases module) quality of life instruments.

The EORTC QLQ-C30 is the core quality-of-life questionnaire of the EORTC quality of life evaluation system *[Bottomlay 2007]*. It has been validated *[Aaronson 1993]* in both English and French and is used on several CCTG studies. The EORTC QLC-C30 consists of 30 items organized into five function domains (physical, emotional, cognitive, role, and social functioning), three symptom scales (fatigue, pain and nausea), six single item scales (sleep disturbance, constipation, diarrhea, dyspnea, appetite loss, and financial issues), and a two item global health status scale. The QLQ-BM-22 module also has been validated specifically in patients with bone metastases and is designed to be used in conjunction with the EORTC QLQ-C30 core questionnaire *[Chow 2009, Zeng 2012b]*. The QLQ-BM22 module consists of 22 items, divided into four sub scales, namely: descriptions of painful sites, painful characteristics, functional interference, and psychosocial aspects. All items are rated from 1 ("not at all") to 4 ("very much") in response to item stems (e.g.; "have you had pain while sitting?"). Items on both the core questionnaire and BM-22 module are scored according to published manuals of the EORTC as routinely used by the CCTG.

The rationale for collecting quality-of-life data on this study, however, is based on two key issues. In the phase III study, quality-of-life information will be used to determine relative benefits of each treatment approach in terms of detectable improvements in pain scores, interference scores, and associated improvements in patients' functional scores. Quality-of-life outcomes will also inform the detection and interpretation of potential adverse effects of treatment such as the impact of vertebral fractures or other adverse effects on Patient Reported Outcomes (PROs). Second, the feasibility of collecting these data using an electronic data capture strategy will be assessed. The feasibility of collecting a typical PRO "battery" (in this case the core questionnaire and module) will inform the design of data collection strategies in future clinical trials conducted by CCTG. The electronic data capture aspect of the protocol is discussed further in Appendix VI.

2.5 Economic Analysis

Spinal bone metastases are a common complication of cancer and often present with spinal bone pain. Progressive disease can lead to soft tissue or bone compressing the adjacent neurological structures, leading to a variety of adverse sequelae. In an effort to improve both clinical outcomes and quality of life over CRT, SBRT has emerged as an innovative treatment option for patients with spinal metastases. Despite the upfront costs associated with planning and delivery of SBRT, the potential benefits include improved quality of life by reducing pain or averting neurological/surgical events. However, there is limited information on the health system costs and outcomes comparing SBRT and CRT in the context of a publically funded health care system

The objective of the economic analysis of the SC.24 CCTG protocol is to compare the costs and utility values of treating spinal bone metastases with SBRT and CRT. The economic analysis will examine efficacy outcomes, health system resource utilization and utility values captured by the study from the publicly funded health system perspective.

Secondary study objectives include: to describe the utility health preference values associated with spinal bone metastases and associated outcomes; to describe and cost the health system resource encounters across both treatment modalities; to describe utilization of analgesics.

2.6 Correlative Studies

Tissue Based Correlative Studies:

Although it has been long established that ionizing radiation (IR) directly kills tumour cells through the induction of DNA double-stranded breaks, it is becoming clear that IR effects on the tumor microenvironment can also influence tumour kill *[Fokas 2012]*. Irradiation of tumours with single high doses of more than 8 Gy result in activation of endothelial cell acid sphingomyelinase (ASMase), and membrane release of the second messenger ceramide, which then initiates endothelial cell apoptosis leading to microvascular dysfunction or ablation *[Fuks 2005; Garcia-Barros 2003]*; ablation of the vasculature can result in secondary tumour cell death. In contrast, lower fractionated doses of IR are not believed to induce significant endothelial apoptosis. Early clinical support for induction of apoptotic mediators by high dose IR is provided by Sathishkumar et al. *[Sathishkumar 2005]*, who demonstrated that elevated ceramide or sphingomyelinase levels in sera correlated with tumour response to high dose irradiation. Ceramide can be metabolized to sphingosine-1-phosphate (S1P), which is a potent pro-survival sphingolipid that can inhibit endothelial apoptosis *[Bonnaud 2007]*. Thus, the balance between pro-apoptotic (ASMase and ceramide), and anti-apoptotic (S1P) factors are intimately involved in regulating endothelial response to high dose IR.

Based on the above, we hypothesize that serum levels of ASMase and S1P will serve as predictive biomarkers for vascular and tumour response to SBRT. To test this, blood will be collected from consenting patients at baseline (prior to first fraction of radiotherapy) and immediately after the second fraction of radiotherapy, and serum and plasma stored. We will assay serum levels of ASMase and S1P, and correlate their levels with clinical response to SBRT. This will lead to the future development and validation of novel serum biomarkers predictive of response to SBRT, which are currently lacking. This may allow for improved stratification of patients in future trials and also support future investigations of novel strategies to biologically enhance tumour response to SBRT.

Image based correlative studies: Radiomics Analysis

Human tumours display substantial inter- and intra-tumoural heterogeneity, on both a genetic and phentotypic level, leading to considerable differences in angiogenic, proliferative, immunogenetic and metastatic potential *[Marusyk 2010]*. Heterogenetic tumours are associated with poorer prognosis in a variety of tumours *[Ganeshan2012a; Ganeshan 2012b; Vujasinovic 2015]*, but is difficult to assess as a biopsy may not be representative of the whole tumour.

With the advent of advanced imaging techniques, radiomics - which refers to the variety of quantitative techniques to evaluate tumour heterogeneity—has emerged as a leading candidate in the evaluation of tumour heterogeneity. Radiomics maximizes the clinical information gathered from imaging, using mathematical methods to evaluate gray-level intensity, pixel inter-relationships, and spectral properties of an image to derive “texture features” which may be imperceptible to the human visual system *[Davnall 2012]*. As it is based on post-processed imaging, the whole tumour can be captured with no need for additional acquisitions. The techniques can also be applied retrospectively, allowing for large cohorts to be studied.

Several different models have been developed, including statistical-, model-, and transform-based methods *[Davnall 2012; Kassner 2010]*. Statistical-based techniques have been most commonly applied and describe the distribution and relationships of gray level values in the image. Statistical-based radiomics include three orders of parameter: first-order statistics relate to gray-level frequency distribution within the region of interest, which can be obtained from the histogram of pixel intensities. Second-order statistics are co-occurrence measurements calculated using spatial gray level dependence matrices and depend on the interaction of its pixel with the neighboring pixels. Higher-order statistics use neighborhood gray-tone-difference matrices, which examine the spatial relationship among three or more pixels and are thought to closely resemble the human perception of the image. Model-based approaches utilizes complex techniques such as fractal analysis to analyse texture features. Lastly, transform-based methods include Fourier, Gabor, and wavelet transports to analyse texture in a frequency or the scale space. The various methods and numerous variables which can be used to extract texture features results in potentially hundreds of values that can be examined.

Studies on radiomics has largely focused on breast, lung, liver and prostate cancer. The results of these works have demonstrated that radiomics can assist with the prediction of disease prognosis *[Segal 2007; Grove 2015]* and treatment selection *[Kuo 2007; Teruel 2014]*. In addition, data has shown that certain radiomic features correlate with molecular processes and genomic expression *[Segal 2007; Diehn 2008]*. However, there is currently little to no literature regarding the texture features of spinal metastases prior to, or after radiation treatment, especially in a randomized controlled trial. SC.24 provides a unique opportunity to explore the use of radiomics in this population to identify prognostic and predictive biomarkers for pain and tumour responses after radiation treatments.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Radiotherapy

3.1.1 *Standard Conventional Radiotherapy (CRT)*

CRT refers to the delivery of radiation to the treatment area with two opposed fields (anterior-posterior parallel opposed pair), and a dose of 20 Gy in 5 fractions. Typically, one to two vertebral bodies above and below the target disease is included to account for technical uncertainties and beam penumbra. This technique does not tissue spare and the entire portal is exposed to the prescribed dose. Standard portals and technology are used and no intensity modulation permitted. This technique and approach represents current Canadian standard of care for radiation of spine metastases.

3.1.1.1 *Adverse Events (CRT)*

The adverse event profile of radiotherapy in general is related to irradiation of normal tissue within the treatment field as well as tumour-specific effects. The most common adverse events include fatigue, soreness, pain flare, skin redness in the irradiated area and damage to other organs within the irradiation field (e.g. dry throat). Less likely adverse events include changes in how temperature is experienced, weakness and clumsiness on one or both sides of the body and episodes of pain or electric shock sensations in the back and legs. Rare but serious side effects include compression fractures and radiation myelopathy which may lead to paralysis or loss to bowel and bladder functions.

3.1.2 *Stereotactic Body Radiotherapy (SBRT)*

This technique has been defined by the Canadian Association of Radiation Oncology (CARO) SBRT Task Force as *"The precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extra-cranial body target with doses at least biologically equivalent to a radical course when given over a protracted conventionally (1.8-3.0 Gy/fraction) fractionated schedule."[Sahgal 2012]*. Essentially, spine metastases are treated with SBRT by applying modern radiation technology, image-guidance and intensity modulation or robotic arc based delivery. The aim is to dose escalate the tumour volume as compared to CRT, while still maintaining safety on the critical organs-at-risk (OAR) by differentially dosing. The dose applied is 24 Gy and delivered in 2 daily fractions. This dose has been reported in series by the study chair and found to be tolerable and efficacious. The intent of spine SBRT is to improve upon the historic CRT rates of complete pain relief and local tumour control.

3.1.2.1 *Adverse Events (SBRT)*

The adverse events anticipated for SBRT are generally the same as for CRT with the exception of radiation myelopathy, pain flare and fracture. Theoretical additional risks associated with SBRT include more intense radiation reactions (e.g. skin, mucosa), which depend upon the radiotherapy field. The most serious risk of spinal SBRT is the occurrence of radiation myelopathy, which can result in permanent paralysis. Recent published guidelines provide safe SBRT dosing to the spinal cord and minimizes this risk to under 5% *[Sahgal 2010; Sahgal 2013b]*; the choice of the experimental arm of this study will account for these. Outcome data utilizing this technique and the published guidelines from the University of Toronto demonstrate good tolerability with no cases of radiation myelopathy *[Sahgal 2013b]*. Single institution experience of the study Chair *[personal communication A Sahgal]* has resulted in no cases of radiation myelopathy in over 1000 treated patients. The second most serious risk is new or progressive vertebral compression fracture (VCF). While this is a known complication of treating bone metastases, its incidence may be greater with SBRT, and has a reported incidence of approximately10% with the treatment regimen of 24 Gy in 2 fractions. Although VCF is diagnosed post-SBRT, still less than half of all patients require an intervention and, in those that did, a minimally invasive cement augmentation procedure has been applied as opposed to an open spinal surgery. Pain flare may also be more intense with this treatment compared to conventional CRT *[Chiang 2013]* and may be treated with prophylactic dexamethasone or rescue dexamethasone upon occurrence.

4.0 TRIAL DESIGN

4.1 Stratification

Patients will be stratified by:

1. Histology (radioresistant♦ vs. radiosensitive♦)
2. "Mass"* on imaging (present vs. absent)
3. Centre

♦ radioresistant are renal cell carcinoma, melanoma, sarcoma and gastro-intestinal; radiosensitive are all other types

* refers to tumour that involves the paraspinal tissues or presence of epidural disease (extra osseous disease extension)

4.2 Randomization

Phase II:

Patients will be randomized to receive one of the following treatments below to a planned sample size of 54.

Phase III:

Patients will be randomized to receive one of the following treatments below to a planned sample size of 228.

Arm	Treatment(s)	Dose	Duration
1	Standard Conventional Radiotherapy (CRT)	20 Gy in 5 fractions	1 fraction a day for 5 days, Monday to Friday excluding weekends (weekend treatments are permitted, if needed)
2	Stereotactic Body Radiotherapy (SBRT)	24 Gy in 2 fractions	1 fraction a day for 2 days, Monday to Friday excluding weekends

5.0 STUDY POPULATION

The study population consists of patients who have MRI-documented spinal metastases and are suitable for receiving radiation therapy.

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed prior to calling for randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Histologic or cytologic diagnosis of cancer (excluding seminoma, small cell lung cancer and hematologic primaries).

5.1.2 Spinal metastasis documented with MRI and suitable for treatment with radiotherapy with the following characteristics:

- Painful, as defined by a pain score ≥ 2 for worst pain in the planned target treatment volume;
- ≤ 3 consecutive spinal segments involved by tumour to be included in the planned target volume. The patient may have other spinal metastases to be treated as per the radiation oncologist's discretion, but the eligible spinal metastatic site for SC.24 has to be one where there is pain and no more than 3 consecutive segments to be included as clinical target volume and appropriate for either 20 Gy in 5 fractions or 24 Gy in 2 fractions per the randomization.

5.1.3 There is no plan to change the pain medication on the first day of protocol treatment with radiotherapy.

5.1.4 ECOG Performance Status 0-2.

5.1.5 Seen by a radiation oncologist and judged to be appropriate for participation in this study including ability to tolerate protocol radiotherapy (SBRT or CRT).

5.1.6 Age of 18 years or older.

5.1.7 Patient is able and willing to complete the Patient Diary (pain and analgesic use).

5.1.8 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life and economic analysis questionnaires in either English or French. The baseline assessment must be completed within required timelines, prior to randomization. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

5.1.9 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

5.1.10 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.11 In accordance with CCTG policy, protocol treatment is to begin within 3 weeks of patient randomization. From the time of successful treatment planning, no more than 12 days can elapse before the first fraction of radiotherapy is delivered.

5.1.12 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Appendix I); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patient will be considered eligible if an ultrasound is negative for pregnancy.

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

5.2.1 Patients who have a pacemaker, such that MRI cannot be performed or treatment cannot be delivered safely.

5.2.2 Patients with prior treatment with any radionuclide within 30 days prior to randomization.

5.2.3 Patients with prior radiation to the spinal segment intended to be treated with protocol radiotherapy such that the protocol therapy cannot be delivered as intended.

5.2.4 Patients with prior surgery to the spinal segment intended to be treated with protocol radiotherapy.

5.2.5 Patients who have received chemotherapy within 1 week prior to administration of protocol radiotherapy or who are expected/planned to receive chemotherapy within one week of completing protocol radiotherapy. Centre guidelines regarding administration of targeted non-cytotoxic therapy must be followed with the proviso that no systemic anticancer therapy should be administered within 24 hours prior to and post-radiotherapy. Endocrine therapy may be administered during radiotherapy as per the discretion of the treating physician.

5.2.6 Patients with spine instability as judged by a *Spinal Instability Neoplastic Score* (SINS) *[Fisher 2010]* of more than 12 (see Appendix III).

5.2.7 Patients with symptomatic spinal cord compression or cauda equina syndrome resulting from bony compression or epidural compression of the spinal cord and cauda equina, respectively. Symptomatic refers to neurologic deficit in the form of motor, bowel or bladder dysfunction

5.2.8 Pregnant or lactating women.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	• Physical Examination • ECOG PS	Within 4 weeks prior to randomization
Radiology	• MRI entire spine	Within 8 weeks prior to randomization
Pain / Analgesic Assessment	• Patient Diary*	Within 7 days prior to randomization ALSO: Repeat at Day 0♦♦
Adverse Events**	Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms): *events ≥ grade 2 only*	Within 7 days prior to randomization
Health-Related Quality of Life***	• EORTC QLQ-C30 and QLQ-BM22 questionnaires	Within 7 days prior to randomization ALSO: Repeat at Day 0♦♦
Economic Analysis***	• EQ-5D-5L questionnaire	Within 7 days prior to randomization ALSO: Repeat at Day 0♦♦
Other Assessments	• SINS score (use scoring sheet♦)	Within 7 days prior to randomization
	• Pregnancy test (for women of child bearing potential only)	Within 7 days prior to randomization
Correlative Studies♦♦♦	• Optional, for consenting patients only: Plasma and Serum	After randomization and prior to start of treatment

* See Appendix VII. Worst Pain to be recorded only for the site included in the radiotherapy target volume. **There must be no plan to change the pain medication on the first day of protocol treatment with radiotherapy (i.e. pain medication previously optimized). The diary MUST capture all medications that affect pain directly (e.g. opioids, non-opioid analgesics) or indirectly (e.g. steroids, co-analgesics).** Other medications may also be listed. Site staff may assist the patient, with listing medication names /routes on the diary.

** **Report only Adverse Events ≥ grade 2**, using the CTCAE v 4.0. See Appendix V.

*** The Quality of Life and Economic Analysis questionnaires will be completed by the patient electronically. See Appendix VI.

♦ See Appendix III.

♦♦ Day 0 is defined as the day of the first fraction of radiotherapy, but *prior* to the administration of radiotherapy.

♦♦♦ See section 13 and the SC.24 Specimen Collection Manual posted on the SC.24 trial webpage.

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the SC.24 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing patients please contact the help desk (link in EDC) or the SC.24 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG SC.24)
- name of investigator under whose name patient will be randomized
- patient's initials (may be coded)
- informed consent language, version date, date signed by patient, name of person conducting consent discussion and date signed by the person who conducted the consent form discussion
- confirmation of the requirements listed in Section 5.0, including dates of essential tests
- stratification factors

7.2 Stratification

Subjects will be stratified by:

1. Histology (radioresistant♦ vs. radiosensitive♦)
2. "Mass"* on imaging (present vs. absent)
3. Centre

♦ radioresistant are renal cell carcinoma, melanoma, sarcoma and gastro-intestinal; radiosensitive are all other types

* refers to tumour that involves the paraspinal tissues or epidural disease (extra-osseous extension)

7.3 Randomization

Randomization will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration/randomization.

All eligible randomized patients will be followed according to the instructions on section 9.0 and Appendix IV for 6 months or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients are as follows: (1) ineligible patients who have received at least one dose of study radiotherapy will be followed the same way as eligible patients (see section 9.0 and Appendix IV); (2) ineligible patients who have received no protocol therapy should submit the Baseline Report plus the 4 week, 3 and 6 month Follow-Up Reports, the latter for the purposes of only reporting patient status and any other anti-cancer therapy received.

8.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 3 weeks of patient randomization. From the time of successful treatment planning, no more than 12 days can elapse before the first fraction of radiotherapy is delivered.

8.1 Treatment Plan

8.1.1 *Radiation Therapy*

Arm	Treatment(s)	Dose	Duration
1	Standard Conventional Radiotherapy (CRT)	20 Gy in 5 fractions	1 fraction a day for 5 days, Monday to Friday excluding weekends (weekend treatments are permitted if needed)
2	Stereotactic Body Radiotherapy (SBRT)	24 Gy in 2 fractions	1 fraction a day for 2 days, Monday to Friday excluding weekends

8.1.2 *Glossary*

CBCT - ConeBeam Computed Tomography
CT - Computed Tomography
CTV - Clinical Target Volume
DRR - Digitally Reconstructed Radiographs
DVH - Dose Volume Histogram
GTV - Gross Tumour Volume
IMRT - Intensity Modulated Radiation Therapy
MLC - Multileaf Collimators
MRI - Magnetic Resonance Imaging
OAR - Organs at Risk
QA - Quality Assurance
PRV - Planning organ at Risk Volume
PTV - Planning Target Volume
SRS - Stereotactic Radiosurgery
VMAT - Volumetric Modulated Arc Therapy

8.2 Radiation Treatment Plan for CRT (ARM 1)

Patients will be simulated and treated with a conventional radiation technique and prescribed a total dose of 20 Gy given daily over 5 fractions, *Monday* to *Friday*, excluding weekends and statutory holidays (if the radiation oncologist wishes the patient to be treated over the weekend or statutory holiday, then this is permitted). The prescribed dose will be to the ICRU point, a prescription isodose or midplane depending on the institutional policy. The beam arrangement of an anterior-posterior parallel opposed pair or a conformal technique using up to 4 beams is allowed at the discretion of the radiation oncologist if a more conformal dose distribution is required to minimize exposure to the normal tissues. No single direct posterior beam arrangement will be allowed nor intensity modulated radiotherapy (IMRT). The target vertebrae will be contoured as the clinical target volume and a 1 to 2 cm margin for PTV and a 1 to 2 cm margin for beam penumbra will be added beyond the PTV to define the field borders. Shielding with MLC or poured lead blocks are permitted and may compromise coverage of the PTV in order to spare the organs-at risk.

8.2.1 *CRT Patient Evaluation*

Patients should be evaluated by the radiation oncologist for suitability for radiation prior to planning. Patients should be able to lie flat and judged able to tolerate treatment. All patients should be reviewed by the treating radiation oncologist weekly during treatment for assessment of toxicity and treatment response.

8.2.2 *CRT Equipment and Treatment Delivery*

8.2.2.1 *Equipment*

Treatment using a standard linear accelerator with beam energies ranging from 6 MV to 18 MV photons is acceptable. Verification of the fields with portal imaging or CBCT is acceptable. Shielding with a MLC or poured lead blocks as beam modifying devices is acceptable. Planning systems with capability for DICOM data transfer must be used.

8.2.2.2 *Treatment Delivery*

Standard fields with a parallel-opposed anterior-posterior beam arrangement and a conformal technique with up to 4 beams is acceptable. No direct posterior beam arrangements will be permitted. No inverse-planned intensity modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT) is permitted.

8.2.3 *CRT Positioning, Immobilization and Localization/Simulation*

8.2.3.1 *Positioning*

Patients will be supine for simulation.

8.2.3.2 *Immobilization*

For spinal metastases below the 5th thoracic vertebrae (T5) no immobilization device is required. For patients with spinal metastases from the 1st cervical vertebrae (C1) to the 4th thoracic vertebrae (T4), a standard thermoplastic head and shoulder mask should be used for immobilization.

8.2.3.3 *Localization Imaging/Simulation*

Thin slice CT simulation as a 3D treatment planning volumetric imaging study must be used to define the target volumes and organs-at-risk (OAR). CT slice thickness of ≤ 3mm is required (pixel size 512 x 512) and should encompass the target vertebrae, and the scan length should be at least 10 cm cranially and caudally. No IV contrast or motion management is required.

If artifacts are present, due to metal prostheses, the artifacts must be contoured and assigned a density of water. The metal implant must also be contoured and assigned an appropriate density.

8.2.4 *CRT Volume Definitions*

8.2.4.1 *Gross Tumour Volume (GTV)*

The GTV will be contoured as visible gross disease on CT. The baseline MRI can be used in the determination of the GTV.

8.2.4.2 *Clinical Target Volume (CTV)*

The CTV will encompass the GTV and include the entire spinal segment to be treated. If paraspinal disease is present then a 0.5 cm margin beyond any paraspinal soft tissue disease will be applied respecting anatomic boundaries. In cases where the adjacent vertebrae above and below needs to be included to achieve the therapeutic goals then a second CTV will be created that includes the target CTV of interest with those levels. No more than 3 spinal segments can be included in that CTV. For example, if T6 is the target vertebrae and the radiation oncologist needs to include T7 as disease is present and judgment made to treat then: a T6 CTV will be contoured and a T6-T7 CTV contoured with the latter considered the final CTV to place PTV margin upon and planned for treatment.

8.2.4.3 *Planning Target Volume (PTV)*

A uniform 1-2 cm PTV will be applied beyond the CTV. The PTV margin applied is based on institution practice. In the case where the target vertebrae includes adjacent levels (per 8.2.4.2) and the target vertebrae CTV drawn, a PTV margin must also be applied to the target vertebrae CTV in order to report dosimetric data; however, the PTV to be planned upon is the multilevel PTV.

8.2.4.4 *Organs at Risk (OAR)*

The spinal canal will be contoured at least 1 vertebral levels above and below the PTV. The only OAR to be contoured for lower thoracic and upper lumbar spinal tumours to be treated are the kidneys.

8.2.4.5 *Nomenclature*

The target CTV vertebrae to be treated and tracked will be named according to the vertebrae to be treated, for example for a T6 target the CTV will be named CTV_T6. The associated PTV will be named the PTV_T6. In cases where adjacent vertebrae (no more than 3 consecutive vertebrae can be included as CTV) is judged by the radiation oncologist to be encompassed in the CTV to achieve the goals of therapy due to adjacent disease, then a new CTV will be created encompassing the vertebrae to be treated. This CTV will be named according to the vertebral levels to be treated, for example if T6 and T7 are to be treated then the CTV will be named CTV_T6T7 and its PTV will be named PTV_T6T7. The treatment plan will be based on this final PTV, i.e. PTV_T6T7. However, a PTV will still be applied to the CTV_T6 and be named PTV_T6 for the purposes of tracking and data collection for the target vertebral segment under study.

8.2.5 *CRT Dose Specification*

8.2.5.1 *Targets*

The total dose of 20 Gy will be delivered in 5 fractions, therefore, 4 Gy per fraction. The total dose will be prescribed to the ICRU reference point, midplane, or an isodose line based on the institutional practice. At least 99% of the PTV should be covered by at least 95% of the prescribed dose (V95%≥99%). A 115% maximum point of the prescription dose is permitted as long as it is not within the spinal canal. In situations where the kidneys require significant shielding, then compromises can be made such that coverage of the PTV by 85% of the prescribed dose is acceptable and the heterogeneity accepted also is adjusted such that we allow 15% to +15% of the prescribed dose. If the PTV extends outside of the external contour, it should be retracted from the external contour by no more than 5 mm for dose statistics.

8.2.5.2 *Organs at Risk*

The maximum dose to the spinal canal will be 22 Gy.

If kidneys are in the field then 1/3 of the contoured kidney may be exposed to the prescribed dose otherwise 2/3 should be shielded by the beam modifying device. There are no other OAR required to be contoured. The spinal canal and kidney dose limits ate strict and as such there are no minor deviations. Any deviation beyond above for spinal canal and kidney are major deviations.

8.2.5.3 *Fractionation*

20 Gy in 5 fractions, therefore 4 Gy per fraction, will be delivered daily Monday to Friday excluding weekends and statutory holidays (if the radiation oncologist wishes the patient to be treated over the weekend or statutory holiday, then this is permitted).

8.2.5.4 *Corrections for Interruptions*

If delays occur in delivery there are no corrections to be applied to the radiation dose delivered.

8.2.6 *CRT Treatment Planning*

8.2.6.1 *Beam Energy*

6MV-18MV photons.

8.2.6.2 *Beam Arrangement*

The beam arrangement must be an anterior-posterior parallel-opposed pair or a conformal beam arrangement with no more than 4 beams.

8.2.6.3 *Beam Modifiers*

MLC or poured lead shielding are acceptable beam modifying devices.

8.2.6.4 *Planning Priorities*

Priorities for planning include: 1) OAR, 2) PTV coverage

8.2.6.5 *Inhomogeneity Corrections*

Inhomogeneity corrections are required when doing final dose calculations.

8.2.6.6 *Acceptable Dose Heterogeneity*

A dose heterogeneity of -5% and +15% of the prescribed dose with the intent to cover at least 99% of the PTV by at least 95% of the prescribed dose is allowed. In situations where the kidneys require significant shielding, then compromises can be made such that coverage of the PTV by 85% of the prescribed dose is acceptable and the heterogeneity accepted also is adjusted such that we allow -15% to +15% of the prescribed dose.

8.2.6.7 *Planning Technique*

Forward planning.

8.2.6.8 *Treatment Delivery Constraints*

Segments are permitted to decrease dose inhomogeneity.

8.2.7 *CRT Verification*

8.2.7.1 *Position Verification/Correction*

Portal images (EPID) or CBCT must be used to verify treatment position as per institutional protocol.

8.2.7.2 *Dose Verification (see ATC Guidelines 13)*

Independent monitor unit (MU) check for the total MU should be ≤ 3% (and for each beams also ≤ 3%) different to the planned MU.

8.3 Radiation Treatment Plan for SBRT (ARM 2)

8.3.1 *SBRT Patient Evaluation*

Patients should be evaluated for suitability of SBRT. Patients should be able to lie flat for at least 60 minutes. In particular, if the pain is too severe when lying down then this may compromise the ability to tolerate SBRT, and if the patients' breathing status is such that lying flat is not possible then the patient is not eligible.

8.3.2 *SBRT Equipment and Treatment Delivery*

8.3.2.1 *Equipment*

Treatment is to be delivered using photons and an energy ranging from 6 MV to 18 MV.
Image-guidance based on CBCT imaging capabilities are required for linac-based delivery.

Planning systems with capability for DICOM data transfer must be used.

Cyberknife, which has a stereoscopic image guidance system and is a well-defined technology specifically for spine SBRT, is permitted in this trial.

8.3.2.2 *Treatment Delivery*

For MLC-linac-based delivery, static MLC, dynamic MLC, compensator IMRT, or VMAT are allowed.

No motion management is required.

For Cyberknife technology, either cone-based or MLC-based Cyberknife deliveries are allowed.

8.3.3 *SBRT Positioning, Immobilization and Localization/Simulation*

8.3.3.1 *Positioning*

Patients will be simulated and treated in the supine position.

8.3.3.2 *Immobilization*

Patients will be immobilized supine only. In a body immobilization device for tumours on and below the 5th thoracic (T5) vertebrae and in a thermoplastic head and neck immobilization mask system for tumours extending from the 1st cervical vertebrae (C1) to the 4th thoracic vertebrae (T4).

The body immobilization device will be according to departmental policy as each center has an established clinical treatment program for spine SBRT, and should be specified in the Facility Questionnaire. In the case of Cyberknife treatments, body immobilization is not mandatory due to the near-real time image guidance verification system inherent to Cyberknife, but for MLC-linac based therapy immobilization is mandatory.

8.3.3.3 *Localization Imaging/Simulation*

Treatment planning CT slice thickness of ≤2.5 mm is required (pixel size 512x512), and the total scan length will encompass the target vertebrae and extend at least 10 cm cranially and caudally. No IV contrast or motion management is required.

MR images for fusion to the planning CT can be obtained from diagnostic imaging without the patient in the simulation position or in the immobilization device. The sequences include a T1- and T2-weighted axial MRI and some centers may use a T1 post-gadolinium axial MRI at their discretion. The target will be contoured according to information on both the planning CT and MRI. The spinal cord will be delineated according to the MRI and the thecal sac delineated according to the MRI and the CT.

If CT artifacts are present, due to metal prostheses, the artifacts must be contoured and assigned a density of water. The metal implant must also be contoured and assigned an appropriate density.

8.3.4 *SBRT Volume Definitions*

8.3.4.1 *Gross Tumour Volume (GTV)*

The GTV is the disease that is visible on the CT and the T1- and T2-weighted axial MR.

8.3.4.2 *Clinical Target Volume (CTV)*

An anatomic approach is taken to the CTV based on where the disease within the spinal segment is located. The rules for CTV are as follows:

1. If the vertebral body is involved with GTV then the entire vertebral body is taken as CTV.
2. If the ipsilateral pedicle and/or transverse process has GTV then the entire ipsilateral posterior segment (pedicle, lamina and transverse process) ±the spinous process is taken into the CTV. The inclusion of the spinous process is per the discretion of the radiation oncologist.

3. If the ipsilateral pedicle, lamina, and/or transverse process has GTV, then the entire ipsilateral posterior segment (pedicle, lamina, and transverse process) plus the spinous process is taken into the CTV
4. If bilateral involvement of the pedicle and/or transverse process with GTV, then the posterior segment anatomy ± the spinous process is taken into the CTV. The inclusion of the spinous process is per the discretion of the radiation oncologist.
5. If bilateral involvement of the pedicles and lamina, and/or transverse process with GTV, then the entire posterior segment anatomy is taken into the CTV, including the spinous process.
6. If the spinous process is involved with GTV alone then the bilateral lamina ± pedicles are to be taken into the CTV.

In addition, the International Spinal Consortium Guideline is a reference for CTV delineation *[Cox 2012]* - see Appendix VIII and can be adhered to as described.

In the case of epidural disease, a 5 mm anatomic margin (excluding the spinal cord) beyond the GTV is required within the epidural compartment including in the cranio-caudal direction. A circumferential CTV as per a donut based CTV is allowed and encouraged in the case of epidural disease at the discretion of the treating radiation oncologist. If paraspinal disease present, a minimum 5 mm CTV margin must be applied beyond the GTV.

In the case of adjacent vertebral segments required to be included in the treatment volume to achieve the goals of care, up to 2 contiguous vertebral segments may be included as a 2nd CTV. For example, when the target vertebral segment for study purpose is C7 then the CTV is named CTV_C7; however, if the radiation oncologist deems it needed to include C6 and T1 then a CTV included the relevant anatomy within all three spinal segments is to be contoured as the treatment planning CTV and named CTV_C6C7T1. For the purposes of the study, the target CTV in this example is the CTV_C7 despite treating CTV_C6C7T1. It would be best to contour each CTV spinal segment separately and then join them to form the treatment CTV.

8.3.4.3 *Planning Target Volume (PTV)*

A uniform margin of 1 to 3 mm is required for PTV. The specific number of millimeters will be center/department policy specific but no more than 3 mm is permitted and no less than 1 mm. In the case where the target vertebrae includes adjacent levels (per 8.3.4.2) and the target vertebrae CTV drawn, a PTV margin must also be applied to the target vertebrae CTV in order to report dosimetric data; however, the PTV to be planned upon is the multilevel PTV. Based on the above example, a PTV_C7 would be generated, as would a PTV_C6C7T1.

8.3.4.4 *Organs at Risk (OAR)*

Each of the OAR limits are strict. There are no minor deviations and any deviation beyond these numbers are major deviations. Please note, in brackets are what the OAR should be called in the plans. This will allow easier analysis of the results.

- Spinal cord (CORD): contoured based on T1 and/or T2 MRI fused to the planning CT. A 1.5-2 mm margin for PRV is to be applied. The thecal sac can also be contoured. The maximum point dose to the spinal cord PRV and/or thecal sac is 17 Gy. This dose is to be strictly adhered to and treatment planning must be adjusted such that this spinal cord PRV/thecal sac dose met within -5%. The point maximum dose to the spinal cord PRV or thecal sac cannot exceed 17 Gy under any circumstance.

- Cauda equine (CAUDA): The thecal sac must be contoured as the surrogate for the cauda equina. The maximum point dose limit of 17 Gy is to be applied to the thecal sac. In this situation no PRV is required. This dose is to be strictly adhered and treatment planning adjusted such that this thecal sac dose met within -5%. The point maximum dose to the thecal sac cannot exceed 17 Gy under any circumstance.
- Kidneys (KIDNEY_RT, KIDNEY_LT): Each kidney will be contoured when relevant to the spinal segment to be treated based on the CT scan. The maximum point dose should be ≤ 26 Gy and the mean dose to each kidney should be ≤ 6 Gy.
- The esophagus (ESOPHAGUS), stomach (STOMACH), rectum (RECTUM), small and large bowel (BOWEL) should be contoured based on the CT where relevant and the maximum point dose should be ≤ 20 Gy.
- Trachea (TRACHEA) should be contoured where relevant on the CT and the maximum point dose should be ≤ 20 Gy.
- The liver (LIVER) should be contoured according to the CT where relevant and the maximum point dose should be ≤ 26 Gy and mean dose should be ≤ 8-9 Gy.
- Each lung (LUNG_RT, LUNG_LT) should be contoured where relevant. The dose limits for each lung are: V10 < 10%, V5 < 35%, and V20 < 3% and a mean dose of ≤ 5 Gy.
- Pharynx (PHARYNX) maximum point dose should be ≤ 20 Gy and mean dose should be ≤ 9 Gy.
- Larynx (LARYNX) maximum point dose should be ≤ 20 Gy and mean dose should be ≤ 9 Gy.
- Each parotids (PAROTIDS_RT, PAROTIDS_LT) mean dose should be ≤ 7 Gy.
- For sacral tumours (S1-S5) nerve roots should be contoured and followed until the point they reach the abdominal contents. A maximum point dose of ≤ 26 Gy is permitted.

8.3.4.5 *Planning Organ at Risk Volume (PRV)*

PRV margin of 1.5-2 mm is required only for the spinal cord and the dose limit of 17 Gy applied to this structure. If the thecal sac is also contoured then the dose limit to the cord PRV is the dose limiting OAR. For cauda equina, the thecal sac is contoured and no PRV applied.

8.3.4.6 *Unspecified Tissue*

A volume known as unspecified tissue must be identified. This volume is defined as tissue contained within the skin but which is not included in any other contoured structure, i.e. external contour with all the target volumes and OAR subtracted. The volume should extend at least 1cm above and 1cm below the most cranial-caudal PTV. The dose should be minimized to this volume using it in the inverse planning objective. There is no constraint for this volume.

8.3.4.7 *Nomenclature*

The CTV and PTV will be named according to the target vertebrae to be treated. For example, for a L1 vertebral segment to be treated, the GTV, CTV and PTV should be named GTV_L1, CTV_L1, and PTV_L1. In the case where non-target vertebrae are to be included in the target volume in order to achieve the goals of therapy, then that target volume includes the vertebral segment of interest plus the additional vertebral segments. That target volume will be named according to the target and the adjacent vertebral segments included (no more than three contiguous vertebral segments can be included). For example, in the case of a L1 vertebral segment to be treated and the T12 and L2 to be treated, then the CTV will be named CTV_T12L2, and the PTV named PTV_T12L2. However, a PTV will still be applied to the CTV_L1 and be named PTV_L1 for the purposes of tracking and data collection for the target vertebral segment under study.

Note for organs at risk that are paired like the kidney then a 'R' or 'L' should precede the OAR name, representing right or left for bilateral organs, e.g. R_kidney where applicable.

8.3.5 *SBRT Dose Specification*

8.3.5.1 *Targets*

24Gy in 2 fractions with be prescribed to the ICRU reference point for the target PTV. Prescription can also be based on an isodose or to the median or mean dose to the PTV and recorded as such.

8.3.5.2 *Unspecified Normal Tissue Dose Limits*

No more than 1cc of unspecified tissue and other normal tissue (excluding those tissues stipulated as OAR) should receive greater than 110% prescribed dose. This is only a suggestion and not a hard constraint.

8.3.5.3 *Fractionation*

24 Gy in 2 fractions, 12 Gy per fraction, delivered daily on Monday to Friday excluding weekend and statutory holidays.

8.3.5.4 *Corrections for Interruptions*

Protocol treatment should be completed within 10 days. If delays occur in delivery there are no corrections to be applied to the radiation dose delivered.

8.3.6 *SBRT Treatment Planning*

8.3.6.1 *Beam Energy*

6MV to 18 MV

8.3.6.2 *Beam Arrangement*

For IMRT, > 6 fields are acceptable and co-planar beam arrangement is preferable. For VMAT, co-planar is preferable but non-coplanar arcs may be accepted. All Cyberknife beam arrangements are acceptable.

8.3.6.3 *Beam Modifiers*

MLC are permitted for linacs. For Cyberknife, its own collimation system is used.

8.3.6.5 *Planning Priorities*

The protocol priorities are: 1) OAR, 2) PTV coverage, 3) Unspecified tissues.

8.3.6.6 *Inhomogeneity Corrections*

Inhomogeneities corrections are required for the final dose calculation.

8.3.6.7 *Acceptable Dose Heterogeneity*

The aim is to maximize coverage of the PTV by at least 100% of the prescribed 24 Gy and to achieve this 80% of CTV should get 100% of the prescribed 24Gy.

A dose heterogeneity of +50% is allowed in the PTV.

8.3.6.8 *Planning technique*

Inverse planning technique should be used and calculation dose grid size must be less than or equal to 0.25cm×0.25cm×0.25cm.

8.3.6.9 *Treatment Delivery Constraints*

For step and shoot IMRT plans, no minimum segment size will be specified, but each centre should follow department policy according to the already existing clinical SBRT protocol. The treatment planning system beam model must have been commissioned such that the monitor units delivered by the minimum segment size can be calculated with acceptable accuracy against measurements. The number of segments per field should be minimized for IMRT (total of 60-90 segments for IMRT plan is reasonable).

8.3.7 *SBRT Verification*

8.3.7.1 *Position Verification/Correction*

Position verification images must be acquired before all fractions. The method must be CBCT for non-Cyberknife systems. Bony anatomy must be matched and residual translations should be < 0.1 cm and rotations < 1º at start of treatment. If the treatment length is longer than 30 minutes (or acceptable time according to centre protocol), or there is any suspect that the patient position may have been changed, intra-fractional scan to check patient position must be done. Fast CBCT (Turbo) protocol should be used if available.

The Cyberknife uses its own stereoscopic imaging system and the spine SBRT protocol should be adhered to for verification.

8.3.7.2 *Dose Verification*

The plan must be verified using an independent dosimetry system such as 2D or 3D diode or ionization chamber array or films. Greater than 95% of measured points meeting the criterion of 3% absolute dose difference and 3mm distance-to-agreement is acceptable. Cyberknife has its own method of dose verification and specifics should be adhered to. A combination of Monte Carlo calculation and a MLC position verification for each patient is allowed.

8.4 Radiotherapy Quality Assurance

The Radiotherapy Quality Assurance process will include four main steps:

- Credentialing for delivery of SBRT and CRT to spinal metastases prior to local activation and at investigator level.
- Prospective Centre Based Individual Pre-Treatment Case Review of treatment plans prior to start radiotherapy for every patient registered on the study.
- Retrospective External Individual Post-Treatment Case Review for all patients after all radiotherapy.
- Planning MRI and dosimetry data submission for quality assurance review.

8.4.1 *Credentialing Requirements*

All centres participating in the study will require credentialing for the delivery of SBRT and CRT to spinal metastases prior to local activation. This credentialing will consist of a Facility Questionnaire and demonstration of the ability to comply with protocol specifications for treatment planning and delivery using anonymized archival data (dummy run).

Credentialing will be mandated for each radiation oncologist investigator, and the site must receive approval from the central QA Reviewer before local activation.

Please review the Radiotherapy Quality Assurance Manual for more details about documents to be submitted, the Facility Questionnaire, timing of the reviews and procedures for documentation uploading. All machines used for SC.24 treatments must be declared by each institution.

8.4.2 *Prospective Centre Based Individual Pre-Treatment Case Review*

The treatment plans will be reviewed for every patient registered on the study. This review will be performed prior to the commencement of radiotherapy by another local radiation oncologist designated for this purpose and identified as study participant, i.e. “local QA reviewer”. The following will be reviewed: contoured volumes, dose summary statistics, dose distributions, and DVHs. Specifications for the review are included in the Radiotherapy Quality Assurance Manual.

8.4.3 *Retrospective External Individual Post-Treatment Case Review*

A final review will be completed for all patients after all radiotherapy has been completed and the required documents submitted (see Radiotherapy Quality Assurance Manual for details).

8.5 Submission of QA Documents for Review

All QA documents will be “uploaded” electronically to a secure website. The SC.24 Central QA Reviewer will access the website to review all QA documents. See the RTQA Manual on the SC.24 CCTG trial specific website for further details.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

9.1 Evaluation During and After Protocol Treatment

Patients will be evaluated during radiotherapy as well as at 4 weeks, 3 and 6 months after the end of radiotherapy.

Investigations		After Treatment
History and Physical Exam including:	• Physical Exam • ECOG PS	As per institutional standards, perform if clinically indicated
Radiology	• MRI entire spine	At 3 and 6 months
Pain / Analgesic Assessment	• Patient Diary*	At 4 weeks and at 3 and 6 months
Adverse Events**	Adverse events ≥ *grade 2* will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).	During radiotherapy treatment♦ and post radiotherapy at 4 weeks and at 3 and 6 months
Health-Related Quality of Life***	• EORTC QLQ-C30 and QLQ-BM22 questionnaires	At 4 weeks and at 3 and 6 months
Economic Analysis***	• EQ-5D-5L questionnaire	At 4 weeks and at 3 and 6 months
Other Assessments	• SINS score (use scoring sheet♦♦)	At 3 and 6 months
Correlative Studies♦♦♦	• Optional, for consenting patients only: Plasma and Serum	Immediately after the **second fraction** of protocol therapy

* See Appendix VII. Worst Pain to be recorded **only for the site included in the radiotherapy target volume**. **The diary MUST capture all medications that affect pain directly (e.g. opioids, non-opioid analgesics) or indirectly (e.g. steroids, co-analgesics) as well as any pre-medications given for the protocol radiotherapy treatment.** Other medications may also be listed. Site staff may assist the patient with listing medication names /routes on the diary.

** **Report only Adverse Events ≥ grade 2**, using the CTCAE v 4.0. See Appendix V.

*** The Quality of Life and Economic Analysis questionnaires will be completed by the patient electronically. See Appendix VI.

♦ Adverse events experienced by the patient during / shortly after radiotherapy treatment, including whether the patient experienced pain exacerbation (Pain Flare) at the treated site, must be evaluated.

♦♦ See Appendix III.

♦♦♦ See Section 13 and the SC.24 Specimen Collection Manual that is posted on the trial webpage.

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Evaluability

Phase II:
The primary outcome measure of the phase II study is feasibility as defined by the ability to accrue 54 patients over an 18 month period (beginning after the first centre is locally activated) to a study that randomizes patients with spinal metastases, and suitable to receive radiation therapy, to Stereotactic Body Radiotherapy (SBRT) or Standard Conventional Radiotherapy (CRT) within a Canadian multicentre setting.

Phase III:
The primary outcome measure of the phase III study is complete pain response in the treatment area at 3 months post-radiation.

Secondary outcome measures include complete pain response in the treatment area at 6 months, radiation site progression-free survival (RSS PFS) at 3 and 6 months, adverse event profile, Health Related Quality of Life and radiotherapy quality assurance (RTQA) compliance.

10.1.1 *Evaluable for Complete Pain Response to Radiotherapy*

All patients who have received at least one dose of radiotherapy and provide complete worst pain score information for the treated site of radiation treatment and opioid analgesic intake information at baseline and at least the 3 month follow up contact will be considered evaluable for response to radiotherapy. Patients will have response classified according to the definitions in Section 10.2.1.

10.1.2 *Evaluable for Radiation Site Progression Free Survival (RSS PFS)*

All patients who have received at least one dose of radiotherapy and have an MRI of entire spine at baseline and at least the 3 month follow up contact will be considered evaluable for RSS PFS. Patients will have RSS PFS assessed as described below in Section 10.2.3.

10.1.3 *Evaluable for the Spinal Instability Analysis*

All patients who have had their baseline SINS score and at least one follow-up SINS score (at either 3 and/or 6 months) assessed will be considered evaluable for the spinal instability analysis.

10.1.4 *Evaluable for Adverse Events*

All patients will be evaluable for adverse event evaluation from the time of their first treatment with CRT or SBRT.

10.1.5 *Evaluable for Quality of Life Assessment*

All patients who have completed a baseline quality of life questionnaire (EORTC QLQ-C30 and QLQ-BM22) and at least one follow-up questionnaire are evaluable for quality of life assessment.

10.1.6 *Evaluable for Economic Analysis*

All patients who have completed a baseline economics analysis questionnaire (EQ-5D-5L) and at least one follow-up questionnaire are evaluable for economic analysis.

10.1.7 *Evaluable for Radiotherapy Quality Assurance (RTQA) Compliance*

Canadian and Australian centres will be evaluable for RTQA compliance from the time they are locally activated to participate on the study.

10.2 Definitions

10.2.1 *Response Outcomes*

Pain response to radiotherapy is based on the International Bone Metastases Consensus Endpoint definitions *[Chow 2002]*.

Complete Pain Response:

A Complete Pain Response is defined as a pain score of zero (0) at the treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent)

Partial Pain Response:

Partial response is defined as any of the following:

i. Reduction in worst pain score of two or more at the bony metastatic site on a 0–10 scale without analgesic increase.

ii. Analgesic reduction of 25% or more from baseline without an increase in worst pain score with reference to baseline.

iii. For patients who were using opioid analgesics at the baseline assessment, a daily oral morphine equivalence of zero (0) without an increase in worst pain score relative to the baseline worst pain score.

Pain Progression:

Pain progression is defined as any of the following:

i. An increase in worst pain score of two or more points above baseline at the treated site without reduction of analgesic use.

ii. An increase of 25% or more in daily oral morphine equivalent compared with baseline, without reduction in worst pain score.

iii. For patients who were not using opioid analgesics at the baseline assessment (daily oral morphine equivalence = 0), consumption of any opioid analgesic without a reduction in worst pain score relative to the baseline worst pain score.

Stable Pain:

Stable pain (SD) is assigned to the remaining evaluable patients, who do not meet any of the categories of Complete/Partial Response and Pain Progression.

10.2.2 *Radiation Site Progression Free Survival (RSS PFS)*

Radiation site progression free survival is defined as the time from randomization to local progression or death.

The response assessment will be an investigator interpretation of the following criteria: lesion status, size, epidural disease extent (Bilsky scale and 3 D measurements), degree of angular kyphosis and height of vertebral body *[Sahgal 2015]*.

Local progression may be defined as:

- Gross unequivocal increase in tumor volume or linear dimension.
- Any new or progressive tumor within the epidural space.
- Neurologic deterioration attributable to pre-existing epidural disease with equivocal increased epidural disease dimensions on MRI.

Biopsy is recommended in those situations in which pseudoprogression due to radiation reaction cannot be ruled out.

10.2.3 *Overall Survival*

Overall survival is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive.

11.0 SERIOUS ADVERSE EVENT REPORTING

This protocol does not contain investigational agent(s), and adverse events occurring as a result of radiotherapy treatment should be reported to CCTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified.

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix V). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information provided in section 3.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol treatment cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the SC.24 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

Within 10 days: Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website

FAX paper SAE Report to:

SC.24 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the SC.24 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

11.3 Other Protocol Reportable Events – Pregnancy Reporting

11.3.1 *Pregnancy Prevention*

Women of Child bearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 5.1.12. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

11.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants or female partners of male participants during treatment. Pregnancies occurring up to 6 months after the completion of radiotherapy must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form, available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health

The CCTG will provide expedited reports of SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

11.5 Reporting Serious Adverse Events to Investigators

CCTG will notify Investigators of all serious adverse events from this trial that are reportable to regulatory authorities in Canada as reported to CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial SC.24 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs will need to be entered into the CCTG trial SC.24 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity (see also Sections 3.1.1.1 or 3.1.2.1).
- Investigator discretion
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Therapy After Protocol Treatment is Stopped

After protocol radiotherapy is completed, further treatment is at the discretion of the investigator. However, according to Section 5.2.5 patients are not expected to receive chemotherapy within one week of completing protocol radiotherapy.

12.3 Follow-up Off Protocol Treatment

All patients will be followed until 6 months after the end of radiotherapy.

13.0 CENTRAL REVIEW PROCEDURES AND SPECIMEN COLLECTION

13.1 Radiotherapy Quality Assurance (RTQA)

RTQA, consisting of (1) credentialing at the investigator level and prior to centre local activation, (2) prospective centre-based review of treatment plans prior to start of radiotherapy for every patient randomized on the study, (3) retrospective external review for all patients after completion of radiotherapy, and (4) planning MRI and dosimetry data submission for quality assurance review, will be required for all patients randomized to the study. See section 8.4 and the SC.24 RTQA Manual posted on the trial webpage for details.

13.2 Central Radiology Review

Central radiology review for the purposes of the radiation site progression-free survival (RSS PFS) secondary endpoint will be required for all patients randomized to the study. The central reviewer will be blinded to study radiotherapy treatment allocation. Please see the SC.24 trial webpage (www.ctg.queensu.ca) for details of electronic upload of MRI files.

13.3 Central Pathology Review

There will be no central pathology review for this study.

13.4 Specimen Collection

The collection of blood is an important part of this trial. Blood will be carefully banked as part of the CCTG tissue bank at Queen's University in Kingston, Ontario.

The blood may be used by researchers now or in the future to develop predictive biomarkers for SBRT. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the blood will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification will be by a patient study number assigned at the time of randomization to the trial and patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

All patients on whom a blood sample is collected will be aware of this retrieval and will have given their consent.

There will be no specimen collection kits provided for this study. Red topped tubes will be used to collect serum and EDTA-lavender topped tubes will be used to collect plasma.

Specimens will be stored at participating centers at -80°C immediately after collection and then batch-shipped (i.e. multiple samples from one site in one shipment) to the CCTG Tissue Bank, frozen on dry ice, for subsequent storage and ultimate analysis. A Specimen Submission Form should accompany all shipments. Details of specimen, collection, processing, packaging and shipping (including the Specimen Submission Form) can be found in the SC.24 Specimen Collection Manual that is posted on the trial webpage.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This study is a randomized multicentre phase II/III study.

The primary endpoint of the phase II study is feasibility of accrual patients to the study, which is defined as the ability to accrue 54 patients over an 18-month period to a study that randomizes patients with spinal metastases to Stereotactic Body Radiotherapy (SBRT) or Standard Conventional Radiotherapy (CRT) within a Canadian multicentre setting.

The primary endpoint of the phase III study is the complete pain response rate at 3 months post-radiation.

Secondary Endpoints:

- Complete pain response in the treatment area t 6 months post-radiation
- Radiation site progression-free survival (RSS PFS) at 3 and 6 months
- SINS score at 3 and 6 months
- Overall survival
- Adverse event profile
- Health-related Quality of Life
- Radiotherapy Quality Assurance (RTQA) compliance

14.2 Primary Endpoints and Analysis

The primary endpoint of the phase II study is feasibility which is defined as the ability to accrue 54 patients over an 18 month period to a study that randomizes patients with spinal metastases to Stereotactic Body Radiotherapy (SBRT) or Standard Conventional Radiotherapy (CRT) within a Canadian multicentre setting.

The primary endpoint of the phase III study is the complete pain response at 3 months post-radiation, which is defined as in section 10.2.1. The analysis of the primary outcome will be based on the intent-to-treat principle, which will include all randomized patients, regardless of whether radiation therapy is given, given as per protocol, or whether there has been fidelity to treatment allocation. Patients that are inevaluable for the primary endpoint due to missing data will be considered as non-responder for the intent-to-treat analysis of the primary endpoint. The primary test will be the Cochran-Mantel-Hanzeal test stratified by baseline stratification factors of Histology (radioresistant vs. radiosensitive) and “Mass” on imaging (present vs. absent), a Chi-square analysis will also be applied to test the complete pain response rates between the two arms, and the 95% confidence limits of the rate difference between the two arms will be evaluated. Logistic regression will be used to estimate the treatment effect while adjusting for unbalanced important factors and to explore factors that are predictive of the complete pain response.

14.3 Sample Size and Duration of Study

For the randomized phase II portion of the study, a convenience sample size of 54 patients is considered sufficient to evaluate whether accrual is feasible. This sample size would also provide an opportunity to estimate the CRT and SBRT 3 month complete pain relief response rates, which would provide the basis for the sample size calculation of the future randomized controlled trial. We chose a sample size that provides for standard error rates in both treatment arms to be less than 10%. Assuming that the CRT response rate is 10% to 30%, with 27 patients, the standard error for the estimated response rate will be 5.8% to 8.8%, respectively. Assuming that the SBRT response rate is about 30% to 50%, with 27 patients, the standard error for the estimated response rate would be 8.8% to 9.8%, respectively.

The trial was activated in July 2015. By November 2016, 44 patients had been enrolled onto the study and the accrual rate indicated that the sample size would be reached in 18 months, thereby meeting the primary objective of the phase II feasibility study. Other metrics of trial conduct were examined including treatment related toxicity and tolerability as well compliance with radiotherapy including quality assurance measures. No safety signals were detected in either arm. Notably, spinal fracture within the treatment fields occurred in 2 patients - both on the conventional treatment arm (CRT). Compliance with protocol mandated radiotherapy and quality assurance measures was high.

Based on the demonstration of feasibility of trial conduct and continued need to critically evaluate the efficacy of SBRT in the treatment of painful spinal metastases, approval was sought and granted in January 2017 for conversion of the study design from a randomized phase II feasibility study to a randomized phase II/III study comparing the two radiotherapy treatment strategies.

Sample size estimate for the phase III controlled trial is with a two-sided 5% level test and 80% power. Based on the results of a randomized phase II trial *[Sprave 2018]* with similar enrollment and radiobiology criteria as the current study, we estimate the complete pain responses will be 20% for the CRT and 40% for the SBRT treatment arms, respectively.

Assuming a 15% drop out/inevaluable rate, we expect the complete pain response rates for the intent-to-treat analysis to be 17% and 34% for the CRT and SBRT arms, respectively. The sample size for the phase III study is 228. Multiple sensitivity analyses will also be performed to further evaluate the results: (i) complete case analysis that excludes those with missing/inevaluable; (ii) multiple imputation analysis that assigns different portions of those missing/inevaluable to be either responders or non-responders. A secondary “as treated” sensitivity analysis will be performed to include only eligible patients who have received protocol-assigned radiation therapy.

Table: Sample Size Parameters for a Subsequent Randomized Controlled Trial

CRT response	SBRT response	Effect size	Drop-out rate	Total Sample Size
10	30	20	0.1	160
10	30	20	0.05	152
15	35	20	0.1	186
15	35	20	0.05	176
20	40	20	0.1	206
20	40	20	0.05	194
25	45	20	0.1	220
25	45	20	0.05	210
30	50	20	0.1	230
30	50	20	0.05	218
10	25	15	0.1	252
10	25	15	0.05	238
15	30	15	0.1	298
15	30	15	0.05	284
20	35	15	0.1	338
20	35	15	0.05	320
25	40	15	0.1	370
25	40	15	0.05	350
30	45	15	0.1	392
30	45	15	0.05	372

This table shows potential sample sizes for the planned RCT study with two-sided alpha = 0.05 and power = 80%. The sample size is very sensitive to the CRT response rate. For example, for an effect size of 20%, if the response rate with CRT is 10%, the sample size will be 160 patients while if the response rate is 30%, the sample size will increases to 230.

14.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office DSMC will review the safety profile of the study radiotherapy every 6 months and investigators will review the data annually at their meetings.

14.5 Interim Analysis

There is no planned interim analysis for the phase III part of the study. A single final analysis will be performed when all patients have met their projected follow-up period of 6 months.

14.6 Secondary Endpoint and Analysis

Complete pain response in the treatment area at 6 months post-radiation. All analyses for the primary endpoint will be performed for the complete pain response at 6 months post-radiation.

Radiation site progression-free survival (RSS PFS) is defined as the time from the date of randomization to the date of documented local progression, as defined in Section 10.2.2; or the date of death. Patients who have not progressed or died by the cutoff date of final analysis, RSS PFS will be censored on the date of the last disease assessment. A Kaplan-Meier curve for proportions of RSS PFS in each treatment arm will be displayed. The RSS PFS rates at 3 and 6 months and their 95% confidence intervals will be estimated. The 95% confidence intervals for the medial RSS PFS will be computed using the method of Brookmeyer and Crowley. The difference in distributions of RSS PFS in the two treatment arms will be compared using the log-rank test stratified by the stratification factors at randomization except study centre. Other potential important factors that predict RSS PFS will be assessed using Cox regression. Overall survival will be analysed similarly.

The incidence of acute severe adverse incidences for each arm will be calculated with its 95% confidence interval, and the analyses will be performed in a tiered comparison, i.e., comparing the overall incidence rates between treatment arms first, then comparison of radiotherapy and disease related symptoms and compared by means of Chi-square analysis or Fisher exact test.

SINS scores will be summarized for data at baseline, 3 and 6 months evaluations. The potential prognostic effects of baseline SINS score on the complete pain response at 3 months post-radiation and the overall survival will be explored using logistic and Cox regression models respectively.

14.7 Quality of Life Analysis

The quality of life (QoL) of patients will be assessed using EORTC QLC-C30 and the Bone Metastases module (BM22) questionnaires.

The EORTC QLQ-C30 is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100.

BM22 has 22 questions consisting of the 4 subscales (painful sites (PS) and pain characteristics (PC) on the symptom scale and functional interference (FI) and psychosocial aspects (PA) on the functional scale). The subscale will also be linear transformed to standardize the raw score to range between 0 and 100.

The quality of life data will be analyzed to look for statistically and clinically significant differences between the study treatment groups. The standard CCTG QoL Response Analysis categorizing patients as either having improved, stable, or worsened QoL will be used as follows [Osaba 2005]. A change in score of 10 points from baseline is defined a priori as clinically relevant. For functional scales and global health status, patients will be considered to have QoL improvement if reporting a score of 10 points or better than baseline at any time of QoL assessment. Conversely, patients will be considered to have worsened QoL if reporting a score minus 10 points or worse than baseline at any time of QoL assessment without above defined improvement. Patients whose scores fall between 10-point changes from baseline at every QoL assessment will be considered as stable. In contrast to functional scales, for the determination of patient's QoL response, classification of patients into improved and worsened categories will be reversed for symptom scales.

14.8 Economic Analysis

The costs and utility values of treating spinal bone metastases with SBRT and CRT will be conducted on the SC.24 data set of patients randomized between SBRT and CRT as treatment for painful spinal bone metastases.

SC.24 compares pain responses as a primary outcome and captures quality of life data using the EORTC QLQC30 and BM22 tools. For the cost-utility analysis, we will collect health system resource utilization data as well as health preference data. Health system resources (e.g. RT planning and delivery details) utilized by patients by treatment modality will be derived from the source documents for SC.24. RT planning costs and health system costs will be derived from provincial sources and publications and will examine events related to treatment outcomes, including changes in pain medication utilization, and sequelae of vertebral body metastases (given the 6 month study follow-up post RT). 2017 Canadian dollars will be applied to resources utilized.

Health preference values will to be collected using the EuroQol (EQ-5D-5L) questionnaire. The EQ-5D-5L will be collected prospectively during treatment and follow-up visits to a subgroup of patients enrolled in the trial. Health preference values have not previously been described in this population or by treatment modality.

EQ-5D-5L is a self-administered questionnaire that consists of two pages comprised of : 1) the EQ-5D-5L descriptive system with five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and each dimension comprises levels (no problems, slight problems, moderate problems, severe problems, and extreme problems); 2) the EQ VAS record of the respondent’s self-rated health status on a vertical graduated (0-100) visual analogue scale. Descriptive analyses will be performed to compare health utility values between treatment arms.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results
CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

16.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

16.3.1 *Obtaining Consent for Pregnancy Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them.

If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up" consent form will not be required by CCTG.

Trial-specific consent forms for "Pregnancy Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner), consent must be obtained from the parent/guardian.

16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at anytime by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 Retention of Patient Records and Study Files

All essential documents must be maintained in accordance with ICH-GCP.

In accordance with GCP 4.9.5, essential documents must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In most cases, this will be for 10 years following the completion of the trial (10 years post final analysis, last data collected, or closure notification to REB, whichever is later) at the centre, or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

16.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

16.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

16.8 Case Report Forms

A list of forms to be submitted as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the SC.24 area of the CCTG website (www.ctg.queensu.ca).

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Prior to Random-ization	After randomization and prior to 1st fraction of RT	Day 0*	Immediately after 2nd fraction of RT	During RT treatment	4 wks post-RT	3 months post-RT	6 months post-RT
History and Physical								
Physical Exam	≤ 4 weeks					As per institutional standards – perform if clinically indicated		
ECOG Performance Status	≤ 4 weeks							
Radiology								
MRI entire Spine	≤ 8 weeks						X	X
Pain / Analgesic Assessment								
Patient Diary	≤ 7 days		X			X	X	X
Adverse Events								
Baseline Symptoms / Adverse Events**	≤ 7 days				X♦	X	X	X
Health-Related Quality of Life and Economic Analysis								
EORTC QLQ-C30 and QLQ-BM22 questionnaires	≤ 7 days		X			X	X	X
EQ-5D-5L questionnaire								
Other Assessments								
SINS score***	≤ 7 days						X	X
Pregnancy Test	≤ 7 days							
Correlative Studies								
Serum and Plasma Collection♦♦		X		X				

* Day 0 is defined as the day of the first fraction of radiotherapy, but *prior* to the administration of radiotherapy

** **Report only Adverse Events ≥ grade 2**, using the CTCAE v 4.0. See Appendix V.

*** See SINS scoring sheet on Appendix III

♦ Evaluation of adverse events experienced by the patient during / shortly after radiotherapy treatment, including whether the patient experienced pain exacerbation (Pain Flare) at the treated site

♦♦ See section 13 and the SC.24 Specimen Collection Manual posted on the SC.24 trial webpage.

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - SPINAL INSTABILITY NEOPLASTIC SCORE (SINS) SCORESHEET

Location • 3 points: Junctional (C0-C2, C7-T2, T11-L1, L5-S1) • 2 points: Mobile Spine (C3-C6, L2-L4) • 1 point: Semi-rigid (T3-T10) • 0 points: Rigid (S2-S5)	Score:_____
Pain relief with recumbency and/or pain with movement/loading of the spine • 3 points: Yes • 1 point: No (occasional pain but not mechanical) • 0 points: Pain free lesion	Score:_____
Bone lesion • 2 points: Lytic • 1 point: Mixed (lytic/blastic) • 0 points: Blastic	Score:_____
Radiographic spinal alignment • 4 points: Subluxation / translation present • 2 points: De novo deformiye (kyphosis / scoliosis) • 0 points: Normal alignment	Score:_____
Vertebral body collapse • 3 points: > 50% collapse • 2 points: < 50% collapse • 1 point: No collapse with > 50% body involved • 0 points: None of the above	Score:_____
Posterolateral involvement of the spinal elements (facet, pedicle or costovertebral joint fracture or replacement with tumour) • 3 points: Bilateral • 1 point: Unilateral • 0 points: None of the above	Score:_____
	Sum Score: _____
Adapted from Fisher 2010. *Interpretation:* • *Sum Score 0 – 6: Stable* • *Sum Score 7 - 12: Indeterminate (possibly impending) instability* • *Sum Score 13 – 18: Instability*	

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection *except* for the Quality of Life instrument and the Patient Diary for which details are as follows:

- The Quality of Life questionnaire data will be entered by the patient on tablet computers, which will be distributed to sites by the CCTG Central Office. For detailed technical and logistical information regarding how to obtain, store and maintain the tablets, as well access and login into CCTG electronic **S**ystem for **P**atient **R**eported **Out**comes (SPROUT) system run by the tablets, please refer to the Electronic Patient Reported Outcome User Guide, posted on the SC.24 webpage area of the CCTG website (www.ctg.queenu.ca)
- The Patient Diary will be completed by the patient on paper and will be subsequently scanned and uploaded into the EDC system as "Supporting Documentation" by the centre CRA

For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the SC.24 area of the CCTG web-site (www.ctg.queensu.ca).

The **electronic** CRFs to be used in this trial, **through the EDC system**, are as follows:

Electronic Folder	Required	To be completed electronically	Supporting Documentation Required[+]
Eligibility Checklist	Prior to randomization	At the time of randomization	Consent form* Pathology report(s) MRI Entire Spine report Patient Diary
Baseline Report	At the time of randomization	Within 2 weeks of randomization	
Correlative Studies Report (Blood)	Continuous Running Log folder	Within 2 weeks after the first sample collection *AND* within 2 weeks after the first sample collection	Consent form*
Radiotherapy Report	At completion of radiotherapy	Within 2 weeks of completion of treatment	
Follow-up Report	At each follow-up visit	Within 2 weeks of completion	MRI Entire Spine report Patient Diary
Relapse / Progression Report	At the time of Radiation Site Progression♦	Within 2 weeks of completion	
Death Report	At the time of patient death**	Within 2 weeks of knowledge of patient's death	Not required unless requested
SAE Report***	At the time of SAE***	Within 24 hours of the event***	Not required unless requested

[+] Scan and upload into the EDC Supporting Document Upload Tool.

* It is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated.

** **Deaths are only to be recorded on the CRFs if they occur within the 6 month study treatment / follow-up period**. Deaths occurring after that time are outside the scope of this study and do not need to be reported.

*** See Section 11.0 Serious Adverse Event Reporting for details.

♦ See Section 10.2.2.

The collection of the following information will ***NOT*** be done through the EDC system. Instead submit as follows:

Data	Required at	Collection /Submission	Comments
Quality of Life Questionnaire	Prior to randomization, Day 0 and at each follow-up visit (4 weeks and 3 and 6 months)	Patient to enter data directly into tablet computers*	Also: site CRA to scan and upload the actual diary to the EDC Supporting Document Upload Tool -
Economic Analysis Questionnaire			
Patient Diary	Prior to randomization, Day 0, and at each follow-up visit (4 weeks and 3 and 6 months)	Patient to complete on paper; site CRA to enter relevant data (as required) in the EDC system within corresponding folders	Also: site CRA to scan and upload the actual diary to the EDC Supporting Document Upload Tool

* See Appendix VI. Please also refer to the Electronic Patient Reported Outcome User Guide, posted on the SC.24 webpage area of the CCTG website (www.ctg.queenu.ca). A paper version of the questionnaire is also available in the SC.24 trial website to be used as a *BACK-UP* in *RARE* cases, if questionnaire completion through the tablet is not possible. If the questionnaires are completed on paper then it should be scanned and uploaded to the EDC Supporting Document Upload Tool and the site CRA should enter the data directly in SPROUT.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be accessed at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

APPENDIX VI - HEALTH-RELATED QUALITY OF LIFE ASSESSMENT AND ECONOMIC ANALYSIS

Introduction

Health-Related Quality of Life Assessment

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Economic Analysis

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, disease free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations;
- to evaluate the extent of change in health benefits of an individual, group, or population across time;
- to evaluate new treatments, technologies, and patient management strategies;
- to support approval of new drug applications or patient management strategies;
- to try to provide the best value for health care dollars within and across diseases and health;
- to compare costs and benefits of various financial and organizational aspects of health care services.

Approval of new therapies or patient management strategies need to consider a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Quality of Life and Economic Analysis Questionnaire.

This study will use the CCTG electronic **S**ystem for **P**atient **R**eported **Out**comes (SPROUT) to collect Quality of Life and Economic data. SPROUT is a web-based, password protected, PIN-restricted system, which facilitates completion of the questionnaires by the patients, through the use of tablet computers, distributed to sites by the CCTG Central Office. The tablets will be equipped with a mandatory lock four-number code which will not be able to be turned off by tablet users. The accounts of the tablets will also be locked and hospital users will be unable to add or remove software or change the settings of the device. Sessions will expire automatically after one hour, if a user remains logged in and the tablet is left untouched. Hospital staff (CRAs) and patients are given access to different screens within SPROUT, and the CRA is automatically logged out of their (set-up) screens before the patient can access their (questionnaire completion) ones. The data entered on the tablet by the patient is not stored within the device, but rather gets imported in real-time directly into the CCTG database, using SSL encryption. Stored data is protected by the CCTG network firewall.

The instructions below are intended as a general guide for the administration of the electronic Quality of Life and Economic analysis questionnaires. The detailed technical and logistical information regarding how to obtain, store and maintain the tablets, as well access and login into the SPROUT system, is provided in a separate Electronic Patient Reported Outcome User Guide document, posted on the trial webpage. The User Guide also provides screen-shots for screens viewed by the patient and the site CRA within the SPROUT system.

1. Preamble

   Quality of life and economic data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self reported questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   Patients may decline answering some or all the questions if they wish to do so. If the whole questionnaire has not been completed, please ask the patient to explain why and document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The CRA should collect the questionnaire (tablet) as soon as it has been completed.

3. Assessments During Treatment

   The quality of life and economic analysis questionnaires should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

   The quality of life and economic analysis questionnaires should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

Because the tablet(s) used to obtain the Quality of Life and Economic data are study-specific and must be shared by all patients in a given centre completion of the electronic questionnaire should occur at the clinic. However, there may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one.

(1) If yes, and the patient is able / willing to come back to the clinic, schedule an appointment as soon as possible after the 'missed' visit when s/he can complete the questionnaire in the tablet kept at the clinic.

(2) If yes but coming back into the clinic is not feasible, then ask the patient if s/he has internet access at home.

a. If yes, proceed to provide the patient with the link to the SPROUT system and the specific PIN number associated with the questionnaire they need to complete. Please also explain that the PIN has an expiration date (provide this date to the patient) and that the questionnaire should be completed before that date.
b. If not, and using the mail is possible, mail a blank paper questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.
c. If not, and using the mail is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers in the tablet kept in the hospital. Make a note that the questionnaire was completed over the phone.

(3) If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation and won't attend the clinic for regular visit(s).

Inquire if the patient has internet access during their vacation. If yes, please provide the patient with the website link to the SPROUT system, the PIN number(s) associated with the questionnaire(s) that need to be completed and written instructions with respect to the date the patient should complete the questionnaire(s). If the patient will not have internet access during their vacation a supply of paper questionnaires, with instructions about when to complete them, and how to return them should be given to the patient to take with them. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may be permitted to complete the questionnaire from home with instructions that it is to be completed the same day. Ask the patient if s/he has internet access at home.

a. If yes, proceed to provide the patient with the link to the SPROUT system and the specific PIN number associated with the questionnaire they need to complete. Please explain that the questionnaire should be completed on the same day.
b. If not, give the patient a blank paper questionnaire, and make arrangements for return of the questionnaire in a timely fashion. When the questionnaire is returned, a comment should be made as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life/Economic Analysis Component

The only time that we will not require a patient to complete the quality of life or economic analysis questionnaires is if s/he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life/Economic Analysis Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life or Economic Analysis Questionnaires (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL/economic assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be noted.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

9. Electronic and Paper Versions of the Quality of Life and Economic Analysis Questionnaires

The patient should complete the Quality of Life and Economic Analysis questionnaires within the SPROUT system. See the Electronic Patient Reported Outcome User Guide, posted on the trial webpage, which provides both the URL for accessing SPROUT, as well as step-by-step instructions for the completion of the electronic questionnaire. However, as it is possible that the SPROUT system may be down, or that access through an electronic device may not be possible, under **rare** circumstances the patient may complete the questionnaire on paper. *If needed*, please obtain the properly formatted paper copy of the Quality of Life and Economic Analysis Questionnaires for this study from the trial webpage and, after the patient completes it, please upload onto the Supporting Documents area of the EDC system (see also Appendix IV of this protocol).

In the pages that follow, the quality of life and economic analysis questionnaires that will be used in this study (combined QLQ-C30, QLQ-BM22 and EQ-5D-5L) have been provided in paper version. The question content of the electronic and paper versions is identical.

Quality of Life Questionnaire – ENGLISH ***PAPER VERSION***

CCTG Trial: **SC.24**

PLEASE NOTE: In this study, Quality of Life data is meant to be provided by the patient electronically, by direct keying of information into a tablet computer. Therefore, this paper questionnaire is *NOT* meant to be used to collect data, and it is only provided as a *BACK-UP* for when, in very rare circumstances, it is not possible for the patient to complete the information directly into the tablet. See Appendix VI of the protocol for more details.

If the paper questionnaire is used, the Clinical Research Associate (CRA) should complete the first (this) page before giving to the patient. After the patient provides the data and the paper questionnaire is returned, the CRA should scan and upload it in the patient-specific Supporting Documents area of the SC.24 Electronic Data Capture (EDC) system.

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

☐ Day 0 (day of first fraction of radiotherapy, *prior* to treatment being given)

After Treatment:

☐ 4 weeks ☐ 3 months ☐ 6 months

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ - __ __ __ - __ __ __ __
dd mmm yyyy

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (SC.24)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week have you had pain in any of the following parts of your body?	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
31. in your back?	1	2	3	4
32. in your leg(s) or hip(s)?	1	2	3	4
33. in your arm(s) or shoulder(s)?	1	2	3	4
34. in your chest or rib(s)?	1	2	3	4
35. in your buttock(s)?	1	2	3	4

During the past week :	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
36. Have you had constant pain?	1	2	3	4
37. Have you had intermittent pain?	1	2	3	4
38. Have you had pain not relieved by pain medications?	1	2	3	4
39. Have you had pain while lying down?	1	2	3	4
40. Have you had pain while sitting?	1	2	3	4
41. Have you had pain when trying to stand up?	1	2	3	4
42. Have you had pain while walking?	1	2	3	4
43. Have you had pain with activities such as bending or climbing stairs?	1	2	3	4
44. Have you had pain with strenuous activity (e.g. exercise, lifting)?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
45. Has pain interfered with your sleeping at night?	1	2	3	4
46. Have you had to modify your daily activities because of your illness?	1	2	3	4
47. Have you felt isolated form those close to you (e.g. family, friends)?	1	2	3	4
48. Have you worried about loss of mobility because of your illness?	1	2	3	4
49. Have you worried about becoming dependent on others because of your illness?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you felt hopeful your pain will get better?	1	2	3	4
52. Have you felt positive about your health?	1	2	3	4

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

Health Utilities Questionnaire – ENGLISH ***PAPER VERSION***

CCTG Trial: **SC.24**

PLEASE NOTE: In this study, Heath Economics data is meant to be provided by the patient electronically, by direct keying of information into a tablet computer. Therefore, this paper questionnaire is *NOT* meant to be used to collect data, and it is only provided as a *BACK-UP* for when, in very rare circumstances, it is not possible for the patient to complete the information directly into the tablet. See Appendix VI of the protocol for more details.

If the paper questionnaire is used, the Clinical Research Associate (CRA) should complete the first (this) page before giving to the patient. After the patient provides the data and the paper questionnaire is returned, the CRA should scan and upload it in the patient-specific Supporting Documents area of the SC.24 Electronic Data Capture (EDC) system.

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

☐ Day 0 (day of first fraction of radiotherapy, *prior* to treatment being given)

After Treatment:

☐ 4 weeks ☐ 3 months ☐ 6 months

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ - __ __ __ - __ __ __ __
dd mmm yyyy

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe 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 doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

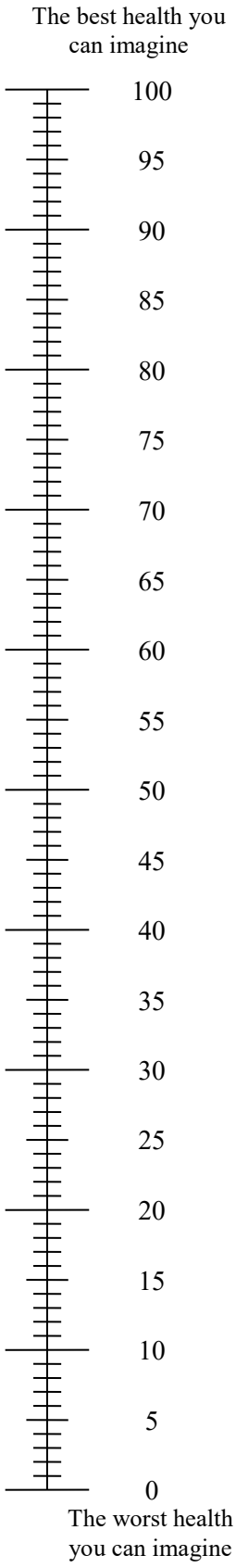
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____
Today's date (Year, Month, Day): _____

Thank you.

CCTG Trial SC.24

A RANDOMIZED PHASE II/III STUDY COMPARING STEREOTACTIC BODY RADIOTHERAPY (SBRT) VERSUS CONVENTIONAL PALLIATIVE RADIOTHERAPY (CRT) FOR PATIENTS WITH SPINAL METASTASES

Patient Initials: _____ - _____ - _____
First *Middle* *Last*

Patient Study ID #: CA__ __ __ __ __ __

Institution: _____

Investigator: _____

PATIENT DIARY

To Whom It May Concern:

The above patient is in a clinical study. In the event of a medical emergency, please telephone one of the individuals listed below:

1. _____ _____
(Name) (Number)

2. _____ _____
(Name) (Number)

To the Patient:

If you have any questions about your diary, please telephone the study nurse or CRA listed below.

_____ _____
(Name) (Number)

Hours of Availability: _____

INFORMATION FOR THE PATIENT

Thank you for participating in this research study.

This document is a diary that you will use to record information needed for this research study. The next two pages contain instructions to help you fill in the diary. The remainder of this document is the diary itself.

You are being asked to complete this diary:

- before you are entered into the study
- on the first day you receive radiotherapy treatment, *prior* to getting the treatment
- 4 weeks after you complete your study radiation treatment
- 3 months after you complete your study radiation treatment
- 6 months after you complete your study radiation treatment

For each time you fill in the diary, you will be asked to give us two types of information for the prior 24 hours:

- your pain **in the area of your spine that was treated with study radiotherapy**,
- how much medication you have taken

If you have any questions, please ask the Clinical Research Associate (CRA) or study nurse at your clinic to help you.

Please go to the next page.

Your Pain

We will ask you about your pain **in the area of your spine that was treated with study radiotherapy**.

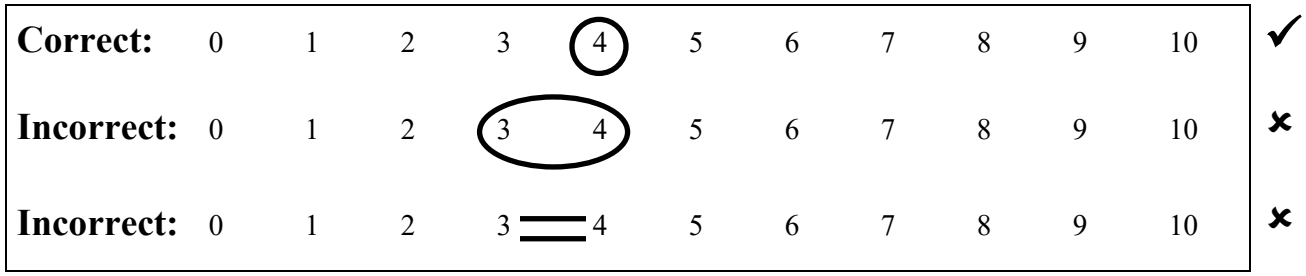
To tell us about your pain, you will be provided with a list of numbers and asked to rate your pain by choosing **one** number from **0 (no pain)** to **10 (pain as bad as you can imagine)** that best describes your pain in the last 24 hours.

This is what that question looks like:

Please rate your pain by circling the **one** number that best describes your pain at its **WORST** in your **spine (area treated with study radiotherapy)** 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

Some correct and incorrect sample answers are shown below:



Please go to the next page

Your Medication

To tell us how much medication you take in the last 24 hours, you will be asked to fill in a table. In most cases, the CRA or study nurse will have already filled in some information about the medications you usually take. For example, if you use 10 mg tablets of Medication A and 2 mg tablets of Medication B, the table will look like this:

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆
Medication A	10 mg	By mouth	
Medication B	2 mg	By mouth	

◆	e.g. If you take 2 tablets in the morning and 2 tablets at night of a particular medication, you took 4 units.
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.
**	For example, medications can be taken by mouth, rectally, or in patch form.

Some correct and incorrect ways to fill in the table are shown below:

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆	
Medication A	10 mg	By mouth	2	✓
Medication B	25 mcg / h	Patch	1 every 3 days	✓
Medication C	2 mg	By mouth	as needed	✗
Medication D	2 mg / mL	By mouth	2 + 1 + 3 = 6	✓
Medication E	5 mg	By mouth	2 or 3	✗

◆	e.g. If you take 2 tablets in the morning and 2 tablets at night of a particular medication, you took 4 units.
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.
**	For example, medications can be taken by mouth, rectally, or in patch form.

Now you are ready to fill out your diary.

If you have any questions or need help, please contact the CRA or study nurse (contact information provided on the cover page).

Thank you for valuable contribution to this research study.

PAIN SCORE AND MEDICATION INTAKE

CRA / Study Nurse *to complete below,* ***in advance****:*
Please check the timing of this diary: ☐ Baseline ☐ Day 0 (day of first fraction of radiotherapy, ***prior*** to treatment being given) ☐ 4 weeks after end of radiotherapy ☐ 3 months after end of radiotherapy ☐ 6 months after end of radiotherapy

Date: _____ - _____ - _____
Day *Month* *Year*

Pain score assessed at:

_____
area of spine treated with study radiotherapy

Please rate your pain by circling the **one** number that best describes your pain at its **WORST** in your **spine (area treated with study radiotherapy)** 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

Please go to the next page.

PAIN SCORE AND MEDICATION INTAKE (continued)

In the following table, please record information for all the medications you took during **the last 24 hours**.

Name of medication	Strength of each unit of medication*	How is medication taken? **	Number of units taken ◆

◆	e.g. If you take 2 tablets in the morning and 2 tablets at night of a particular medication, you took 4 units.
*	A unit of medication is a tablet or capsule, a millilitre (mL) of liquid, a suppository, or a patch.
**	For example, medications can be taken by mouth, rectally, or in patch form.

If you wish, you can write down any other medications you have taken today here:

_____

_____

If you wish, you can write down any symptoms you are having here:

_____

_____

You have now completed the Patient Diary for THIS time point.

Bring the diary to your next clinic visit

Thank you for your valuable contribution to this research study.

APPENDIX VIII – CTV DELINEATION

Target volume outlining

Several publications may inform contouring for spine lesions with the International Spine Radiosurgery consortium guidelines ([8] shown below) the most widely used.
Clinical Treatment Volume (CTV) should be defined as per diagram below.

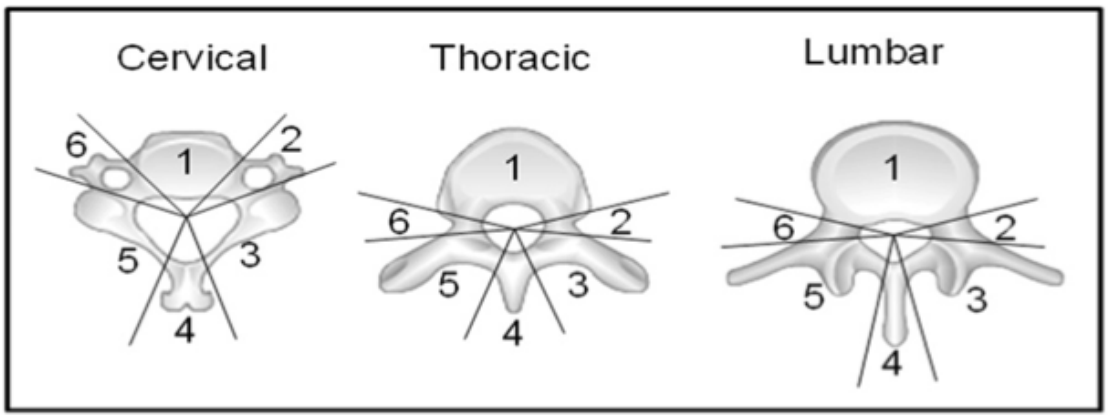


Table 3 Guidelines for spinal SRS bony CTV delineation

GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1, 2	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
GTV involves unilateral pedicle	2	2, 3 ± 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body
GTV involves unilateral lamina	3	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3, 4, 5	Include entire spinous process and bilateral laminae

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; ISRC = International Spine Radiosurgery Consortium.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Maaike Hum Study Coordinator CCTG Email: mhum@ctg.queensu.ca or: Dr. Wendy Parulekar Senior Investigator CCTG Email: wparulekar@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Arjun Sahgal Study Chair Email: Arjun.Sahgal@sunnybrook.ca	416-480-4834	416-903-0456
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Wendy Parulekar Senior Investigator CCTG or: Maaike Hum Study Coordinator CCTG	613-533-6430	613-533-2941