Protocol Title: A Phase II Pilot Single Arm Prospective Clinical Trial of Rapid Institution of Helical TomoTherapy-based Radiation Therapy for Patients with Painful Osseous Metastatic Disease

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A Phase II Pilot Single Arm Prospective Clinical Trial of Rapid Institution of Helical TomoTherapy-based Radiation Therapy for Patients with Painful Osseous Metastatic Disease

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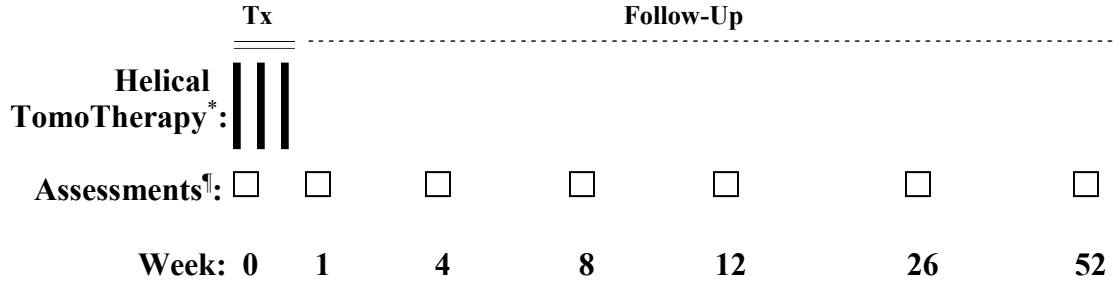

*2-5 Helical TomoTherapy radiation treatments over 1-2 weeks
¶ Physical Exam (PE) and/or surveys
Treatment-related toxicity will be captured during treatment PEs and follow up PEs.

STUDY OVERVIEW

- Eligible patients with 1-3 painful osseous metastases will receive a consultation and subsequently undergo CT simulation, radiation treatment planning, and their first radiation treatment on day 1.
- Patients will receive a total of 2-5 fractions of high dose palliative radiation therapy via helical TomoTherapy consisting of 5-10 Gray (Gy) per fraction with a minimum biologic effective dose (BED) of 25 Gy.
- Standard patient-specific treatment planning quality assurance will be performed on a cylindrical phantom with ion chamber and film measurement.
- Software provided by TomoTherapy Inc.® will be used to measure the radiation exiting the patient and recalculate the dose the patient received. This calculated dose will then be compared to phantom measurements and treatment planning calculations to validate the ability of this novel radiation dose verification software to verify the accurate delivery of radiation. This will not replace standard quality assurance measurements.
- At the Emily Couric Cancer Center, an in-house developed infrared motion tracking system will monitor patients' positions for any deviation from the treatment position. This is not standard of care but may augment standard safety measures with full implementation in the future and does not subject the patient to any risks or discomfort. Infrared motion tracking is will be optional and not required for patients treated at CRH.

- Contouring (the demarcation of the tumor and critical structures) will be performed in the standard manner for treatment planning.
- Contouring will also be performed in an expedited, experimental manner on diagnostic image sets which will then be compared to the standard contours. Experimental contouring will not replace standard contouring, nor affect treatment planning.
- Patients will complete questionnaires to capture pain scores of the treated lesion(s), analgesic use, patient functional status, patient quality of life, and patient satisfaction at 1 week, 4 weeks, 8 weeks, 12 weeks, 6 months, and 12 months following treatment. These scores will be compared to questionnaires completed pretreatment.
- Radiation-induced toxicities will be captured during treatment physical examinations and at follow-up physical examinations at 4 weeks, 12 weeks, 6 months, and 12 months.

ELIGIBILITY (see section 3.0)

- Patient has a biopsy proven diagnosis of cancer. The osseous metastatic lesions do not need to be biopsied.
- Patients with multiple myeloma are eligible for the study.
- Patient has 1-3 major painful osseous metastases (target lesions) from any primary cancer or unknown primary cancer.
- Long bone target lesions must have a Mirels fracture score of ≤ 7 (**See Appendix G**).

- Patients with spinal cord compression from vertebral body metastases are not eligible.
- Target lesions have not previously been treated with external beam radiation.
- Radiation oncologist determines that the patient is medically able to undergo palliative radiation therapy.
- Patient has target lesions that are radiographically consistent with metastatic disease on CT, MR, or PET CT obtained within 8 weeks of treatment.
- Persistent distinguishable pain associated with target sites to be treated.
- Patient average bone pain index (BPI) pain score for last 72 hours at specified location is $\geq$ 3 (0-10 scale)
- Patients may have additional non-painful or minimally painful osseous metastases (if patient has pain from additional sites, the pain from the additional sites must be evaluated as being less intense by at least 2 points on the BPI compared to the site(s) treated)
- The patient may have previously been treated with external beam radiation therapy to other body sites, but not to the target lesions.
- The patient may have previously or currently be undergoing chemotherapy or bisphosphonate therapy.
- The patient will be able understand English (or a medical interpreter for their native language must be available for all study visits).
- 18 years of age or older.
- Life expectancy > 12 weeks.
- Able and willing to answer simple survey questionnaires.
- Able and willing to keep a logbook of analgesic use (with or without assistance).
- Willing to return to clinic for follow-up visits after treatment.
- Signed study-specific informed consent form

TREATMENT (see section 4.0):

- Patients will receive 2 to 5 palliative radiation treatments prescribed to 5-10 Gy per treatment with a minimum biologic effective dose (BED) of 25 Gy. Radiation dose will be determined and prescribed by the treating radiation oncologist based on tumor volume, proximity and dose to adjacent critical structure limitations, tumor radiosensitivity, whether the patient is receiving systemic chemotherapy, and the overall performance status of the patient.

CORRELATIVES:
None

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

Background: Osseous metastatic disease causes significant pain, decreased functioning, and decreased quality of life. Progressive bone destruction can lead to pathologic fractures or spinal cord compression leading to orthopedic surgery, paralysis, and/or patients becoming bedridden. Opioids can alleviate pain but have neurologic and gastrointestinal side effects that further decrease quality of life. Radiation therapy can effectively reduce pain and opioid use and prevent further bone destruction, however, its use is limited because the current workflow frequently requires one week for planning and two weeks for delivery. Additionally, typical palliative radiation plans for osseous metastases lack conformality of dose to the tumor volume, and therefore, result in radiation-induced toxicity to large volumes of adjacent normal tissue. Recent software and hardware advancements provide the opportunity to revolutionize the palliative treatment of osseous metastases. We propose to investigate a novel TomoTherapy-based workflow, called STAT RT, which includes same day CT simulation, treatment planning, and quality assurance measurements coupled with highly conformal treatment delivery for patients with osseous metastases in a pilot clinical trial.

Objective: The overall goal of this STAT RT proposal is to develop a more rapid, convenient, and effective palliative radiation approach for patients with osseous metastases that is less toxic and less expensive than current treatment regimens. We have already optimized the conformality of TomoTherapy-based radiation doses for osseous metastases, and we have developed a STAT RT workflow that condenses standard of care simulation, planning, quality assurance, and treatment delivery into 5-6 hours. Additional optimization and integration of new radiation therapy computing processes will allow for real time simulation, planning, and delivery via a novel Scan-Plan-Treat STAT RT workflow that will ultimately require only 30 minutes. In this study we will evaluate the effectiveness of the current STAT RT workflow, and we will investigate techniques for further optimization that will be needed to create a 30 minute Scan-Plan-Treat STAT RT workflow.

Primary Specific Aim/ Hypothesis: We will quantify the time for pain relief, amount of pain relief, opioid use reduction, functional scores, quality of life, and satisfaction of patients treated with STAT RT for osseous metastases. We hypothesize that these patients will have rapid and significant pain relief, improved quality of life, and high patient satisfaction.

Secondary Specific Aim/ Hypothesis: We will optimize the integration of commercially available and in-development software to develop the Scan-Plan-Treat STAT RT workflow. Specifically, we will A) optimize rigid and deformable co-registration of pre-contoured diagnostic image sets to MVCT simulation scans and compare the accuracy to the same pre-contoured diagnostic image sets co-registered to kilovoltage CT (kVCT) simulation images and then

kVCT simulation to MVCT scan co-registration, B) optimize CT-detector-based exit dose measurement algorithms for quality assurance and compare to standard of care phantom-based quality assurance, C) explore the options of including an in-house real time infrared tracking system for intrafractional patient position monitoring to ensure accurate patient treatment. We hypothesize that these new components will provide effective and efficient methods for treatment planning, quality assurance, and patient position monitoring that can be used in a future 30 minute Scan-Plan-Treat STAT RT workflow.

Study design: We will recruit 30 cancer patients with 1-3 painful osseous metastatic lesions (target sites) who are candidates for palliative radiation therapy. Patients will receive 2-5 fractions of 5-10 Gy (minimum BED of 25 Gy) of conformal radiation therapy delivered to the target sites via the Helical TomoTherapy system using the STAT RT workflow. Data will be collected to evaluate the effectiveness of our novel image co-registration techniques and CT-detector-based exit dose calculations. These novel techniques for image co-registration, radiation dose calculations, and possible patient position monitoring will not alter or replace standard of care techniques. Using validated surveys we will record patient pain, analgesic use, function, quality of life, and patient satisfaction prior to treatment and at 1 week, 4 weeks, 8 weeks, 12 weeks, 6 months, and 12 months after therapy. Radiation-induced treatment related toxicities will be captured during treatment and at the above time points.

1.2 Disease Background

1.2.1 Epidemiology of Metastatic Bone Disease

The American Cancer Society estimates that approximately 1.5 million people in the United States will be diagnosed with cancer, and 560,000 will die of cancer in 2010 (1). These numbers are projected to increase rapidly in the near future due to national demographics with a large number of Americans reaching retirement age over the next 15-20 years, resulting in a doubling of projected new cancer diagnoses in 2050 to 3 million (2). Most cancer deaths involve extensive locoregional tumors or metastatic disease to brain, lung, liver, or bone causing pain, disability, and decreased quality of life. As treatments for cancer improve, patients are living longer with advanced cancer than ever before, and the management of metastatic disease is becoming increasingly more multi-disciplinary and complex with patients treated simultaneously with systemic therapy, surgery and radiation.

The skeleton is one of the most common sites of metastatic disease and is often the first site affected by metastases (3, 4). It was estimated that in 2004, 250,000 cancer patients were afflicted with metastatic bone disease (3). Bone metastases are most common in patients with multiple myeloma, of whom 90% develop bone metastases (5). Approximately 70% of patients dying of breast and prostate cancer have evidence of metastatic bone disease, and bone metastases are also common in thyroid, kidney, and lung cancers, occurring in 30-40% of these cancers (4). Metastatic bone disease causes considerable morbidity in patients

with cancer, resulting in pain, hypercalcemia, pathologic fractures, compression of the spinal cord or cauda equina, and spinal instability (4).

1.2.2 Standard Palliative Radiotherapy Techniques

Bone metastases are the most common cause of cancer-related pain (4). It is well documented that cancer-related pain is often inadequately controlled in the palliative care setting, and both the pain and opioid medication interfere with patient function and quality of life (6-8). Radiotherapy is an important tool for the alleviation of pain and suffering for cancer patients, and it is used to prevent pathologic bone fractures or palliate tumor-induced obstruction, bleeding, and pain that is not well palliated with pharmacologic treatment (9). Bony metastatic lesions in the spine and extra-axial skeleton are often targeted with radiation, resulting in prevention of pathologic fractures, reduction in pain, and improvement in quality of life (10-13).

a) Lack of Dose Conformality

For 30-40 years, standard palliative radiotherapy treatment techniques have utilized simple opposed beam arrangements such as treating a patient with parallel opposed anterior and posterior beams. Although simple to plan and deliver, such techniques provide poor conformality, and large volumes of organs at risk (OARs) may receive the full prescribed dose depending on the level treated. **See Figure 1.** These OARs may include (skin, lung, esophagus, trachea, stomach, small, bowels, rectum, bladder, or genitals) resulting in cough, dysphagia, odynophagia, nausea, vomiting, weight loss, fatigue, diarrhea, dysuria, erythema, and pruritus of the skin and genitals (13, 14). Despite being planned and delivered on sophisticated systems, these treatments are frequently only modestly effective, and cause significant toxicity to an already ill patient population with a limited life expectancy (13).

b) Slow Workflow for Treatment Planning and Quality Assurance

Conventional simulation and treatment planning is performed over a several day process prior to the first delivered treatment. The patient generally is first seen in consultation and scheduled for a CT simulation on a subsequent day. During the CT simulation the patient is placed in the position in which they will ultimately be treated on a linear accelerator (LINAC) or TomoTherapy unit, and immobilization and support devices are fabricated after which they undergo a CT scan in the treatment position. He or she must then wait, sometimes several days, for the contouring of the CT simulation images (a process by which the radiation oncologist specifies the planning target volume (PTV) of the tumor to be treated and the regional organs at risk (OARs) or adjacent tissues that may receive radiation resulting in toxicity). Following the contouring of the CT images, radiation treatment planning is performed, during which time medical dosimetrists and physicians determine the beam angles and treatment technique to deliver the prescribed dose to the PTV while attempting to minimize dose to OARs if possible. Again, for standard osseous metastatic disease palliative techniques

tend to be fairly simple. Following treatment planning, quality assurance calculations and/or measurements are performed by medical physicists before delivery of the first treatment to ensure accuracy of delivering the planned dose and ensure patient safety.

c) Inconvenient, Modestly Effective Treatments

Although fractionation schedules in Europe are trending toward hypofractionation (fewer treatments), the most common palliative dose fractionation schedules in the USA for osseous metastases vary between 20 and 30 Gray (Gy) in 5 -10 fractions delivered over 1 -2 weeks (15). Conventional radiotherapy, regardless of fractionation schedule, has been found to be modestly effective in palliation of bone metastases, resulting in an improvement in pain in only about 60% of patients (16, 17). In a retrospective study of end stage cancer patients receiving palliative radiotherapy, Gripp et al found that half of the patients received treatment for >60% of their final days of life (18). Thus, these often modestly effective treatments subject the patients to repeated visits to the treatment center and consume precious time and energy for ill patients and their families. Clearly it is important that we design more effective palliative treatments that are more efficient to plan and deliver, minimize acute toxicity, and require fewer total treatments.

1.2.3 Costs of Metastatic Bone Disease

The treatment of metastatic bone disease is costly. Schulman and Kohles estimated that the mean per patient direct cost for cancer patients after diagnoses with metastatic bone disease was $75,329 compared to $31,455 for cancer-matched controls without metastatic bone disease (3). Using this data, the authors estimated that the national cost burden for patients with metastatic bone disease was $12.6 billion in 2004, which was 17% of the NIH-reported $74 billion direct medical costs for cancer (3). These costs will clearly increase with our aging population and associated increase in cancer prevalence (2). From a societal standpoint, looming Medicare financial constraints will likely result in reduced reimbursement for palliative services, driving the economic incentive to develop the next generation of more clinically efficient palliative radiotherapy workflows.

1.3 Study Agent(s) Background and Rationale

1.3.1 Stereotactic Body Radiotherapy (SBRT): A more effective, highly conformal hypofractionated palliative radiation technique

In the search for more effective and less toxic radiotherapy techniques, much attention has been focused on stereotactic body radiotherapy (SBRT). SBRT is the use of hypofractionated, highly conformal, high dose radiation delivery that has been modeled after intracranial stereotactic radiosurgery (SRS). Like SRS, SBRT uses multiple beams that converge on the target volume. This minimizes the volume of tissue receiving high dose to where the beams intersect, reducing dose to normal tissue. This allows for the delivery of ablative doses of radiation in a few fractions with acceptable toxicity (19, 20). SBRT is a proven

method for treating lung cancer, yielding excellent rates of local control for non-small-cell lung cancer and resulting in 5-year survival rates potentially comparable to that of surgery (20, 21). In addition, the treatment of liver metastases with SBRT has yielded promising results, achieving local control rates at 2 years of approximately 70–90% (22-24).

SBRT has also been used in the palliative treatment of bone metastases to the spine with remarkable success. Multiple studies have used SBRT to safely deliver high doses of radiation to the spine while significantly limiting dose to the spinal cord and achieving local control rates of > 80% at one year (25-29). Fractionations in these studies have ranged from 1 to 5 fractions delivering 4- 24 Gy per individual fraction, with total doses between 10 to 30 Gy (25-29). In the largest prospective study of spine SBRT by Gerszten, 336 cases were treated primarily to relieve pain, and they achieved significant pain improvement in 290 patients (86%). Nelson, Tsai, Gibbs, and Ryu, have also reported pain reduction in greater than 80% of patients in their studies (25-30), much improved over the 60% in conventional radiotherapy (16, 17). Not only do more people experience pain relief, but the pain relief is more durable. Gagnon demonstrated statistically significant improvement in pain scores lasting throughout all 4 years of follow-up (31). Ryu found the median duration of pain relief to be 13.6 months with SBRT (30), which is a dramatic improvement compared to the average 3 to 6 months of palliation with conventional therapy (13, 32). Additionally, spinal SBRT treatments have been effective in achieving local control in tumors typically resistant to radiotherapy, such as renal cell carcinoma and melanoma, due in part to radiation injury to the tumor vasculature (25, 28, 30, 31).

1.3.2 Adverse Events with SBRT: Minimal Toxicity

Though great success is seen in high dose, hypofractionated therapy, care must be taken to avoid incorrectly delivering the high dose radiation to normal tissue. Prevention of damage to normal tissue is ensured through careful patient immobilization, co-registration of multiple diagnostic imaging modalities (MRI, PET CT, contrast enhanced CT) to the kVCT simulation to accurately define the target and OARs, inverse treatment planning with the use of intensity modulated radiation therapy (IMRT), patient-specific quality assurance, and CT image guidance at the time of treatment delivery. Nevertheless, common side effects of radiotherapy do occur with SBRT as do other adverse events. However, the advantage of conformal radiation is that it spares radiation dose to normal tissue. This has been demonstrated by reports of little to no toxicity in many trials using SBRT(25, 31), and is reinforced by the findings of McIntosh et al, who compared conformal helical TomoTherapy with conventional 3D conformal treatment techniques on an anthropomorphic phantom and showed that helical TomoTherapy significantly improved conformality and reduced dose to regional critical structures(33).

Most significant adverse events in spinal SBRT have occurred with treatments that used extremely high-doses (>20 Gy) in a single fraction. Gomez et al reported odynophagia and dysphagia in 1 patient who had received 22Gy to the esophagus in a single dose, and another patient developed an esophageal ulcer and necrosis after receiving 24Gy to his esophagus in one fraction (34). Another patient developed bronchial stenosis after receiving 11Gy to a bronchus. In another study with similarly high dose fractionation schedules, 39% of patients treated with 18 to 24 Gy in a single dose developed new or progressive vertebral fractures (35). However, their patient selection did not utilize a scoring system to identify patients at high risk for pathologic fracture, such as the Mirels scoring system (36). In contrast, Gagnon et al, using mean doses of 26 Gy in 3 fractions in 200 patients, only had 2 patients (1%) develop vertebral fractures (31). Sahgal et al reported 5 cases of radiation myelopathy and concluded that for single fraction SBRT, up to 10Gy to a maximum point to the thecal sac is safe (37). Dose distributions that cause such severe toxicities described above will not be used in this study. Our study will use doses similar to those used by Gagnon for his SBRT studies that reported remarkably low toxicities. Additionally, to minimize the number of patients who develop new or progressive fractures, we will use the Mirels scoring system to identify patients at high risk of fracture and exclude them from the study (36).

1.3.3 Extrapolation of Spinal SBRT-like Dose Distributions to Non-spine Osseous Metastases

Given the advances in radiation delivery with SBRT and its success in palliation of spine metastases, it is logical to apply these advancements in technology to extra-axial bone metastases; however no trials have been published to date. This is due to the fact SBRT is only reimbursed for limited indications such as spinal metastases. It is fair to hypothesize that the extrapolation of SBRT-like dose distributions to extra-axial bone metastases will improve pain control and that rapid institution of radiation will minimize the time patients are in pain and on high dose opioids that place them at risk for iatrogenic medical complications. By applying the concepts of spinal SBRT for palliative treatment of non-spinal bone metastases, we propose to use highly conformal radiation therapy techniques to treat patients that will allow increased dose per fraction and fewer total fractions with less toxicity compared to standard non-conformal palliative regimens. **See Figures 1-2**.

Figure 1: Conventional Technique

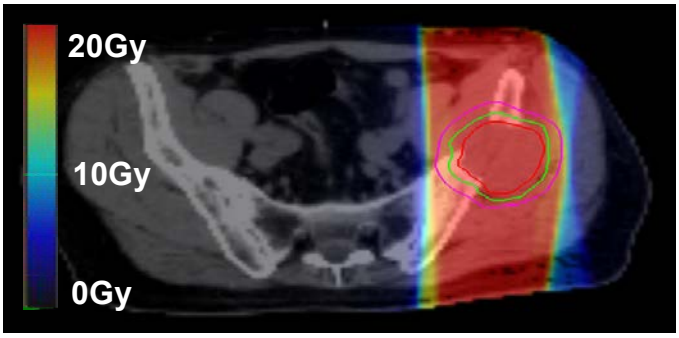
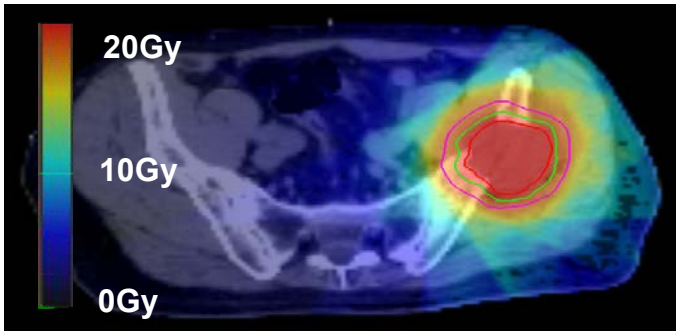


Figure 2: Conformal Technique



1.3.4 Relative Biologic Effective Dose: a method to compare different dose fractionation schedules

Based on the linear-quadratic equation, one can calculate the biologic effective dose (BED) to compare dose delivery of different fractionation schedules using the equation: BED = nd [1+d/(alpha/beta)], where n = number of fractions and d = dose per fraction. As seen in **Table 1**, when compared with conventional fractionation schedules for palliative osseous metastases, such as 30Gy in 10 fractions or 20Gy in 5 fractions, high dose per fraction regimens deliver very similar BED to early responding tissues and slightly higher BED to late responding tissues. Our study will deliver a minimum BED of 25 Gy to each treatment target. We anticipate that most patients on this trial will receive 2-3 treatments with 8 Gy delivered per treatment, however, the dose per treatment, number of treatments, and total dose will depend on patient-specific factors including tumor histology, tumor location and proximity to critical OARs, and tumor size. Relative BED provides a method to compare different dose fractionation schedules that can be used to correlate the treatment with patient outcomes.

Table 1: Comparison of BED in Different Fractionation Schedules

	Total dose	# of Fractions	Dose per fraction (Gy)	alpha/beta	BED
Early Responding Tissues	30	10	3	10	39
	20	5	4	10	28
	24	3	8	10	43
Late Responding Tissues	30	10	3	3	60
	20	5	4	3	47
	24	3	8	3	88

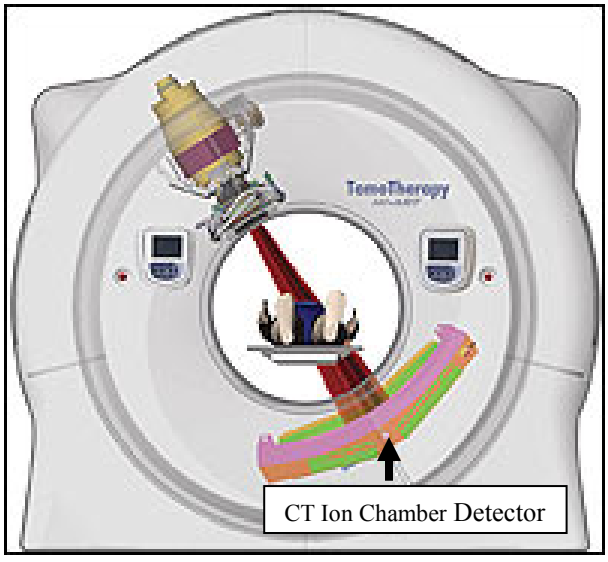
1.3.5 STAT RT: A Rapid Palliative Radiotherapy Workflow

The University of Virginia Radiation Oncology Department has received institutional funding through an institutional Buchanan Grant and a CMS Innovation Award to fund the technical development of a TomoTherapy-based STAT RT program for rapid pain palliation. We have already treated over 30 patients in the first phase of development of this program with a STAT RT workflow that compresses the standard workflow to 6 hours allowing same day simulation, treatment planning, and treatment delivery. In the second phase of development we will optimize the combination of several recent computing advancements to create a Scan-Plan-Treat STAT RT workflow in which CT simulation, treatment planning, and treatment delivery with real time quality assurance will be performed on a single system in approximately 30 minutes.

1.3.6 Technologic Rationale For The Choice of The TomoTherapy Platform

TomoTherapy delivers highly conformal and homogenous dose distributions through modulation of dose from a bank of 64 binary 6.25-mm-wide collimator leaves capable of pneumatic opening or closing 51 times per revolution as the gantry revolves around the patient **See Figure 3**. The system can also treat patients with discrete beam angles (i.e. the radiation beam not rotating) in a mode called TomoDirect. Due to increased costs for IMRT, this treatment technique is not allowable for the treatment of non-spine bone metastases. Although all TomoTherapy treatment delivery is technically IMRT, the treatment planning can be done in either a 3D or IMRT mode allowing highly conformal treatments to be billed as 3D and thus used in the treatment of all patients with bone metastases. In addition, good preliminary data exists to support the use of the fan beam MVCT as a CT simulation image set for treatment planning and the use of CT detector-based exit dose methodology for quality assurance, making this system an excellent platform to pilot this research.

Figure 3: Helical TomoTherapy Unit



1.3.7 STAT RT Workflow: Same Day CT Simulation, Treatment Planning, Treatment Delivery

As previously stated, we have already developed a STAT RT workflow for same day palliation that requires approximately 6 hours, and is a highly coordinated conventional workflow with kVCT simulation, treatment planning, treatment plan quality assurance, and then delivery of conformal hypofractionated radiotherapy. All treatments are planned and delivered on FDA-approved systems. We have treated over 30 patients to date with this workflow, and preliminary results reveal rapid and durable palliation with minimal acute toxicity. This workflow allows patients to receive an entire course of palliative treatment from start to finish in 1 to 5 days, a process that conventionally takes 3 weeks. Since patients are billed for each individual treatment, requiring fewer treatments reduces health care costs in addition to being more convenient. With the STAT RT program we are now able to offer a unique workflow that delivers rapid, effective, and efficient palliative radiotherapy that is cost effective, less toxic, and more convenient for cancer patients and their families. The dose conformality of these treatments is excellent and will not be further optimized. In this pilot clinical trial, for the primary specific aim we will quantify patient outcomes following treatment with the current STAT RT workflow in an effort to determine its benefits and risks to patients. As a secondary aim, we will systematically evaluate and optimize the software necessary for the clinical implementation of the more efficient Scan-Plan-Treat STAT RT workflow.

1.3.8 Scan-Plan-Treat STAT RT Workflow: A Novel and More Efficient STAT RT Workflow

With recent advances in software and technology, we plan to further condense the STAT RT workflow into the Scan-Plan-Treat workflow, a 30-minute process in which all steps (MVCT simulation, diagnostic image co-registration, treatment planning, and treatment delivery with real time quality assurance) are performed on the TomoTherapy unit. This advanced workflow will eliminate the need for the patients to undergo a kvCT simulation on a separate unit as well as make it unnecessary for the patient to leave the treatment table between the simulation and treatment.

1.3.9 Secondary Aims: Requirements For Clinical Implementation of the Scan-Plan-Treat STAT RT Workflow

1) MVCT simulation image acquisition (10 minutes) then rigid or deformable image co-registration of existing diagnostic image sets with pre-contoured target and OAR volumes to the MVCT simulation scan for contour transfer (3-5 minutes).
2) Rapid inverse treatment planning (3-5 minutes).
3) **Monte Carlo secondary dose calculation (2-3 min)**
4) At the Emily Couric Cancer Center location, simple real-time patient motion tracking via infrared cameras to ensure accurate patient setup during MVCT

simulation and treatment delivery (concurrent). No data for this aim will be collected at CRH.

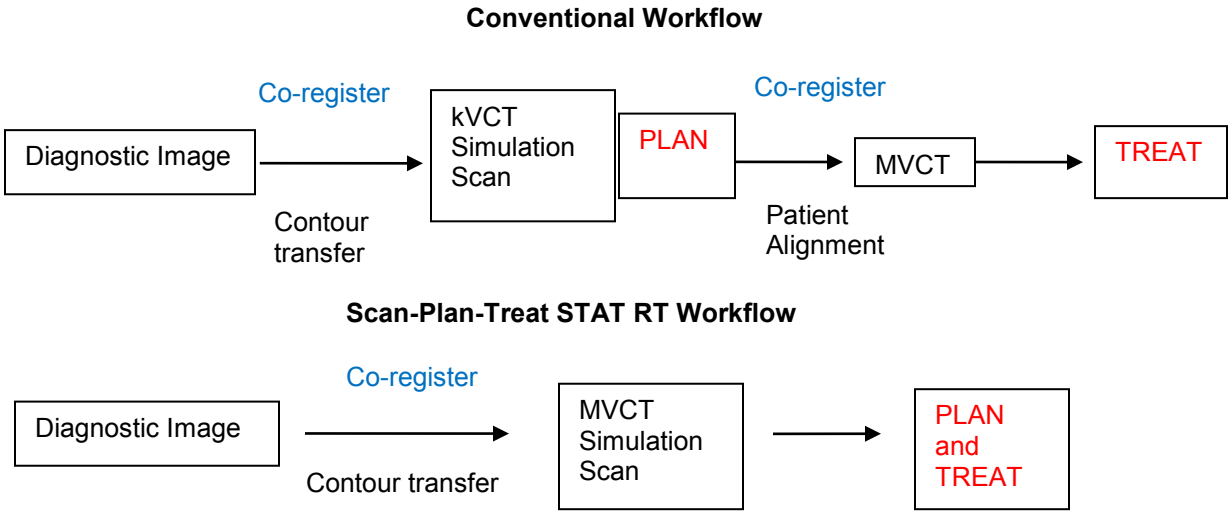
5) Patient-specific quality assurance using CT detectors during treatment delivery (10 minutes).

1. New image co-registration workflow

In the conventional workflow, target volumes and OARs are contoured on recent diagnostic images (MRI, PET-CT, or diagnostic CT that are already available in the patient's electronic radiology chart). After the patient undergoes a kVCT simulation, the contoured diagnostic images are rigidly or deformably co-registered to the kVCT simulation images, and the contours are transferred. This allows for high resolution diagnostic images to be used for tumor and normal tissue identification, which is not always possible to differentiate on CT simulation scans due to the resolution of standard wide bore CT simulation scanners. Multiple commercial image processing systems are available for this image processing, and we are currently using Velocity® (Atlanta, GA) image processing software. Following treatment planning, the patient then undergoes image guided treatment delivery, a process in which a daily MVCT scan is obtained on the TomoTherapy unit and co-registered to the planning kVCT scan. Patient setup shifts can then be made to ensure accurate patient setup, and the patient is treated. Therefore, this is a two image co-registration workflow. **See Figure 4**.

A kVCT simulation scan has historically been used for simulation in the conventional workflow for both palliative and curative radiation planning. Compared to MVCT scans, it has higher resolution and allows the possibility for administration of iodinated IV and/or GI contrast, which makes it easier to identify soft tissues and bony anatomy for treatment planning. However, contrast agents are not generally given for kVCT simulations of patients for palliative treatment of osseous metastases since the soft tissue and bone windows are adequate. MVCT scan soft tissue and bone windows have quite reasonable resolution and can easily be co-registered to higher resolution diagnostic studies for contour transfer. MVCT scans are routinely co-registered to kVCT scans for image guidance on a daily basis. Our preliminary data suggests that the optimization of this one step image co-registration workflow of diagnostic image sets to a MVCT simulation scan is clinically similar to the conventional two image co-registration workflow.

Figure 4: Comparison of Image Co-Registration Workflows



2. Rapid inverse treatment planning on MVCT scans

CT image sets are used for radiation treatment planning because the electron density of tissues, which is required for calculating dose, is easily determined based on the Hounsfield units. The tissue electron density determination is essentially the same for MVCT and kVCT scans. It has previously been reported that as far as the dose calculations are concerned, treatment planning on either a kVCT simulation image set or an MVCT simulation image set yields treatment plans that are within 1% of each other(38).

We have recently published that the TomoTherapy STAT RT treatment planning module can calculate SBRT and palliative treatment plans in just a few minutes(39). The computing speed of radiation treatment planning systems is about to take a quantum leap forward with the incorporation of new algorithms that will take advantage of the replacement of central processing units with graphic processing unit's whose more rapid and parallel calculating potential can improve treatment planning speed by 10-20 times(40, 41). Real time inverse treatment planning of IMRT or 3D TomoTherapy plans has not been a problem for patients treated with STAT RT to date. We will compare planning times for current FDA-approved treatment planning systems as well as for newer, in-development GPU-based algorithms.

3. Fast Monte Carlo based secondary dose calculation

Most treatments delivered on a traditional linear accelerator undergo a secondary dose calculation before the patient is treated. The secondary calculation is compared to the dose calculated by the treatment planning system and must be within agreement before the treatment can be administered. With the addition of Quan Chen to the research team, UVa now has access to a very fast secondary dose calculation algorithm specifically designed for TomoTherapy. Using this Monte Carlo based software, all treatment plans will be second checked for dose calculation accuracy.

4. Optical tracking methods for patient intra-fractional motion monitoring

Consistent patient positioning during CT image acquisition and treatment is critical to ensure accurate dose delivery. Physical immobilization devices such as external body frames, aquaplast masks and other body molds, and vac-lock vacuum bags are commonly used to ensure patient positioning reproducibility. X-ray or CT image guidance prior to radiation delivery on the treatment unit is routinely employed in the clinic. Methods for optical tracking of markers on the patient surface or of the patient's skin surface are available to ensure consistent patient positioning after image guidance and during treatment, known as intra-fractional motion (42, 43). This provides a method without ionizing radiation for confirming patient position that can be used real time during the treatment process. With this information, treatment can be paused if the patient's position changes during treatment. At the Emily Couric Cancer Center, we have developed an inexpensive in-house optical tracking system to monitor patient positioning real time that we will optimize in this protocol. Culpeper Regional Hospital does not have this imaging capability and patients treated on this protocol at CRH will not have optical surface tracking.

5. Novel CT-detector-based quality assurance methodology

Current standard of care TomoTherapy quality assurance methodology requires that each patient-specific treatment plan be delivered to a cylindrical plastic phantom with ion chamber and film measurement or an array of radiation detectors to ensure geometric and dose accuracy to within ± 3%. However, this method does not measure the dose that the patient is receiving during treatment or provide full 3D dose verification. It causes another delay in delivering the first treatment to the patient as it requires approximately 30-40 minutes to complete, and is generally done by a medical physicist after clinical patient care is finished. A methodology to monitor the patient exit dose in real time would increase patient safety through verification of daily treatment accuracy as well as expedite the treatment workflow. Clearly, a real-time quality assurance methodology that does not require moving the patient off the TomoTherapy treatment couch for phantom measurements is essential for the development of a 30-minute Scan-Plan-Treat workflow. Current dose verification methodologies measuring dose at the time of patient treatment are limited to point measurements on the patient surface (44), which is rarely in the target volume or a critical OAR, or though

expensive implanted dosimeters (45, 46) which are not practical for most palliative patients. Since there is not a method to directly measure the three dimensional dose in the patient, alternative approaches are being developed and tested in academic clinical settings. These alternative approaches reconstruct the delivered three dimensional dose distribution based on the measurement of either entrance or exit dose and back-projecting the measurements onto simulation or image guidance CT image sets.

The opportunity to reconstruct dose from information collected during treatment became available with the incorporation of radiation imaging detectors, such as electronic portal imaging devices (EPID) on linear-accelerators and CT detector arrays on TomoTherapy. Dose reconstruction using in-line EPID was first described by McNutt et al (47, 48). The EPID, when deployed during treatment, collects exit fluence from the patient and then back-projects this to X-ray fluence before entering the patient; then, the dose in the patient is re-computed using this entrance fluence and the planning CT images. However, there are many limitations to EPID-based dose verification. For example, the EPID was originally designed for semi-quantitative portal imaging; and for the purpose of dose reconstruction, it suffers from a narrow dynamic range, short life span, non-linearity in the dose response, ghost artifacts from low temporal resolution, and cross-plane scatter photon contribution to the measured fluence (49). Investigators are currently working on methods to overcome these challenges.

The TomoTherapy unit has an in-line source-patient-detector geometry with CT ion chamber detectors that are used for daily MVCT scan image guidance for accurate patient positioning that remain in place during both imaging and treatment. **See Figure 3**. These CT detectors can also be used to measure the patient exit dose fluence and back-project this onto a planning CT scan for volumetric or 3D dose reconstruction. Dose verification on TomoTherapy was first studied by Kapatoes et al., who calculated the entrance fluence from the exit dose using a transfer matrix, which is calculated based on the radiological path length from the source to the detector (50, 51). The use of a CT ion chamber array has multiple advantages over EPID for exit fluence measurement. It is more durable, and has a much longer life span. It has a wider dynamic range and doesn't limit treatment positions. Finally, it is less sensitive to the noise from cross-plane scatter photons that complicate EPID-based dose reconstruction (52). Our recently published preliminary data showed that the current TomoTherapy CT-detector based algorithm for dose reconstruction is robust with +/- 3-5% accuracy which is well within the acceptable range for clinical care (53). We will collect clinical data and continue to optimize this in-development software.

One drawback from the dose reconstruction method mentioned above is that it relies on the accurate knowledge of the patient geometry and attenuation at the time of the treatment. This information may not be fully available nor accurate. This leads to the ambiguity in determining whether a discrepancy observed from the dose reconstruction is real (caused by the machine) or merely an artifact caused by the patient such as weight loss or

positional changes. To remedy this, we have developed a method to detect if the multi-leaf collimator (MLC) is open or close based on the sharp change in the exit fluence independent of the patient attenuation (54). In addition, the LINAC output and gantry angles during treatment are measured independently for quality assurance. Combining those data, the impact of deviations during the treatment delivery can be evaluated through the MCL dose calculation. The CT detector clinical data collected will also be used to optimize this in-development software.

1.4 Preliminary Studies

We have performed significant preliminary research into optimizing each of the necessary steps for clinical implementation of the Scan-Plan-Treat STAT RT workflow as detailed below. Preliminary clinical data will be collected from patients treated with STAT RT on this protocol to optimize the software required to develop the more efficient Scan-Plan-Treat STAT RT workflow. A Scan-Plan-Treat workflow will not be used on this clinical protocol.

1. Preliminary Clinical Outcomes of Patients Treated with STAT RT

We have treated approximately 30 cancer patients with a conformal hypofractionated STAT RT treatment regimen for a variety of palliative indications. We have treated patients with IMRT and 3D TomoTherapy planning modes and have extensive experience using the TomoTherapy planning systems for optimizing conformality of the radiation. Retrospective review of these patients shows that the majority of them have had rapid and durable palliation of symptoms with minimal toxicity (unpublished data). In general, patients are extremely satisfied with the speed at which their treatment is initiated and the convenience of the hypofractionated regimens.

2. Preliminary Studies for Scan-Plan-Treat STAT RT implementation

a) New image co-registration workflow

FDA-approved imaging software for rigid and deformable co-registration and transference of target and OAR contours from diagnostic image sets to either kVCT or MVCT images is commercially available. We are using Velocity® image processing software. Our preliminary unpublished data confirms that the MVCT scan has sufficient resolution, particularly of bone anatomy, for accurate co-registration to contoured diagnostic images and that this one step co-registration process yields comparable agreement to the conventional two step image co-registration workflow with +/- 2-3 mm differences. **See Figure 4.** This level of agreement is consistent with results reported from image co-registration studies performed on a multi-institutional pediatric clinical trial with co-registration data of 51 patients from 45 institutions using 11 different image software systems. They reported an inherent uncertainty of 2 mm for MRI to CT co-registration (55). MVCT image guidance scans and kVCT simulation co-registration occurs routinely in the clinic and only takes a few seconds, therefore,

we do not believe that this will be a rate limiting step in the clinical implementation of the Scan-Plan-Treat STAT RT workflow.

b) Rapid inverse treatment planning on MVCT scans

We have shown that accelerated treatment planning software for Helical TomoTherapy provides clinically acceptable dosimetry, with conformality and homogeneity that is superior to standard LINAC-based 3D conformal planning and is only slightly inferior to standard Helical TomoTherapy dosimetry (33). We have also shown that, with planning times of 2-5 minutes, this accelerated treatment planning software provides levels of dosimetric conformality, heterogeneity, and avoidance of organs at risk for simple SBRT treatments that are clinically equivalent to those generated with conventional Helical TomoTherapy treatment planning(39). This preliminary data supports that treatment planning speed in not likely to be rate limiting in the ultimate clinical implementation of the Scan-Plan-Treat STAT RT workflow.

c) Monte Carlo secondary dose calculation

We have clinically implemented a validated software second dose calculation check that reads TomoTherapy treatment plan information exported through DICOM and then performs a Monte Carlo dose calculation in a few minutes. Our preliminary results show a 3D-dose distribution can be calculated within 2-5 minutes (56). The software has been used clinically for 8 months on all patients treated on TomoTherapy at UVA with excellence results.

d) Novel CT-detector-based quality assurance methodology

Our pre-clinical evaluation of the CT-detector based exit radiation dose verification algorithm has been retrospectively studied by Sheng et al using in-development software (53). We compared with planned and delivered doses with the conventional phantom quality assurance measurements for 24 patients and 347 treatment fractions. The concordance of planned to delivered dose calculated by the in-development software was shown to be ± 5% (53). This tolerance is within the standard of care of other current clinically available quality assurance methods. We are also using the CT detector exit dose data to measure the MLC leaf opening time and comparing this with the calculated leaf opening time as a novel quality assurance methodology.

e) Optical tracking methods for patient intra-fractional motion monitoring

At the Emily Couric Cancer Center, we have recently developed an in-house optical tracking system using multiple OptiTrack FLEX:V100 cameras (Natural Point, Corvallis, OR). **See Figure 4**. The camera utilizes 26 infrared light-emitting diodes (LEDs) and a charge coupled device (CCD) to capture the reflective light from markers with special coating. By using multiple cameras, the 3D position of each reflective marker can be determined precisely. Three reflective markers are fixed on a rigid body marker base that can vary in size from a few centimeters to much larger and create a “trackable” that can easily be placed on a patient’s surface to track their motion. **See Figure 5**. The x, y, z, yaw, pitch

and roll of the trackable can be detected by the camera system. An in-house C program was developed to stream the data and display the position of the trackable in real time. Multiple trackables can be placed on a patient and monitored simultaneously. In the lab, localization precision of 0.1 mm was achieved (unpublished data). Through strategic positioning of the trackables, movements of the head, neck, and extracranial locations can be closely monitored. This optical tracking technology is unique to ECCCC and is not available at CRH and patients treated at CRH will not undergo this experimental aspect of the trial.

Figure 4: OptiTrack Camera

Figure 5: Trackable

1.5 Rationale for Study Design

As explained in the previous sections, conventional palliative radiotherapy for bone metastases offers only often modestly effective treatments that subject the patients to repeated visits to the treatment center and consume precious time and energy for ill patients and their families. With the STAT RT workflow, we hypothesize that we can offer more effective palliative treatments that are more efficient to plan and deliver, minimize toxicity, and require fewer total treatments. We are conducting this investigator initiated prospective pilot clinical trial to 1) evaluate the effectiveness and patient satisfaction with STAT RT for patients with painful bone metastases, and 2) optimize those components of the workflow needed to create a 30 minute Scan-Plan-Treat STAT RT workflow . Further development for this workflow has federal funding via a three- year 2012 CMS Innovation Challenge Award .

Primary specific aim: Quantify the time for pain relief, amount of pain relief, opioid use reduction, functional scores, quality of life, and satisfaction of patients treated with STAT RT for osseous metastases.

The objective of palliative treatment is to relieve pain, improve function, and improve quality of life. These will be measured before and after treatment with the following endpoints:

- The Brief Pain Inventory (BPI) is a proven survey to evaluate pain levels of patient's with metastatic bone pain and their responses to treatment (57).
- Patients will keep an analgesic use logbook and have their doses converted into Oral Morphine Equivalent Doses (OMED). In this way we can track changes in their opiod requirements.
- Treatment response will be measured by the guidelines set forth by the International Bone Metastases Consensus Group (58). They have established a method to measure response to palliative RT accounting for opiate use. These responses are categorized as: Complete Response, Partial Response, Pain Progression, Stable Pain. See Section 6.1.1 for details about this categorization.
- The FACT-G and FACT-BP questionnaires are proven measures of quality of life for people with painful bone metastases (59).
- Karnofsky Performance Score (KPS) is a proven measure of functional status.

We hypothesize that the convenience of the STAT RT workflow will result in high patient satisfaction. The FACIT-TS-BTCSQ survey has been shown to be an effective tool in measuring the satisfaction in patients being treated for metastatic bone disease (59). Therefore, we have modified this tool to suit our patient population, and we will use this survey to measure patient satisfaction at each assessment.

Toxicity will be assessed by CTCAE Version 4.0 and RTOG Late Radiation Morbidity Scoring Criteria. These are common criteria used to asses the toxicity associated with radiation therapy. The CTCAE will assess acute toxicity, and the RTOG Late Radiation Morbidity Scoring Criteria will assess late toxicity, which is defined as toxicity that occurs 3 months or more after treatment.

Secondary Specific Aim: Optimize the integration of commercially available and in-development software to develop the Scan-Plan-Treat STAT RT workflow.

As described in the background, this optimization will require:
1) rapid co-registration of diagnostic images onto MVCT simulation images for accurate contouring and treatment planning
2) real-time patient-specific quality assurance using CT detectors during treatment delivery
3) real-time patient motion tracking to ensure accurate patient setup during MVCT simulation and treatment delivery.

To implement rapid co-registration of diagnostic images onto MVCT simulation images into the workflow, we must first confirm that this image and contour-transferring method is just as accurate as the conventional method. Again, the experimental method requires rigid and deformable co-registration of

pre-contoured diagnostic image sets to MVCT simulation scans; and in the conventional method, pre-contoured diagnostic image sets are co-registered to kilovoltage CT (kVCT) simulation images, and then kVCT simulation images are co-registered to the MVCT scan. **See Figure 4.** Contours generated from these two different registration flows will be quantitatively compared as described in detail in Section 7.1.

Earlier we described the advantages of using the CT detector on the TomoTherapy unit with dose verification software to provide near real time 3D dose verification. We must confirm that the use of the CT detector and dose verification software yields equivalent results to conventional phantom-based quality assurance. Thus, exit radiation dose measurements and back-projected dose recalculation verification software will be compared to standard pretreatment phantom quality assurance measurements. If we prove the doses calculated by both methods to be equivalent, we could rely on only the CT detector and dose verification software for quality assurance in the future, which would further streamline the workflow.

As described in the background and preliminary studies, our in-house infrared tracking system has been developed to monitor patient positioning during simulation and treatment delivery. This infrared tracking system will be validated by 10 healthy volunteers and then used to monitor patient motion during treatments at the Emily Couric Cancer Center. The effectiveness of the infrared tracking system will be determined by comparing its position calculations with the position changes as determined by the position of the treatment set up lasers with respect to the patient's set up skin marks before and after treatment. Patient tracking is an additional experimental quality assurance process that in no way affects the patient's treatment and will not be implemented at Culpeper Regional Hospital at this time.

1.6 Correlative Studies

Not Applicable

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

Our primary objectives are to quantify outcomes of patients with osseous metastases treated via the STAT RT workflow. Specifically, we are plan to:

2.1.1 Estimate the response to palliative radiation as defined by International Bone Metastases Consensus Group using the BPI and OMED to categorize into Complete Response, Partial Response, Pain Progression, and Stable Pain after receiving treatment via the STAT RT workflow.

2.1.2 Estimate the change in the patient's quality of life and function as scored by FACT-BP and KPS after receiving treatment via the STAT RT workflow.

2.1.3 Estimate patient satisfaction with the STAT RT workflow using a modified FACIT-TS-BTCSQ survey.

2.1.4 Report the treatment-related toxicity using CTCAE Version 4 and RTOG Late Radiation Morbidity Scoring Criteria after receiving treatment via the STAT RT workflow.

2.2 Secondary Objectives

Our secondary objectives are to optimize the integration of commercially available and in-development software that are needed to develop a Scan-Plan-Treat STAT RT workflow. Specifically, we plan to:

2.2.1 Optimize CT-detector-based exit dose measurement algorithms for quality assurance and compare them to traditional phantom quality assurance methods.

2.2.2 Optimize rigid and deformable co-registration of pre-contoured diagnostic image sets to MVCT simulation scans and compare the accuracy to the conventional method in which the same pre-contoured diagnostic image sets are co-registered to kilovoltage CT (kVCT) simulation images and then kVCT simulation is co-registered to the MVCT scan.

2.2.3 Validate an in-house infrared tracking system and monitor patient motion during treatment for all patients treated a ECCCC.

2.3 Exploratory Objectives

Not applicable.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Patient has a biopsy proven diagnosis of cancer. The osseous metastatic lesions do not need to be biopsied.

3.1.2 Patients with multiple myeloma are eligible for the study.

3.1.3 Patient has 1-3 major painful osseous metastases (target lesions) from any primary cancer or unknown primary cancer.

3.1.4 Long bone target lesions must have a Mirels fracture score of ≤ 7 (**See Appendix G**).

3.1.5 Radiation oncologist determines that the patient is medically able to undergo palliative radiation therapy.

3.1.6 Patient has target lesions that are radiographically consistent with metastatic disease on CT, MR, or PET CT obtained within 8 weeks of treatment.

3.1.7 Persistent distinguishable pain associated with target sites to be treated.

3.1.8 Patient average BPI pain score for last 72 hours at specified location is ≥ 3 (0-10 scale)

3.1.9 Patients may have additional non-painful or minimally painful osseous metastases (if patient has pain from additional sites, the pain from the additional sites must be evaluated as being less intense by at least 2 points on the BPI compared to the site(s) treated)

3.1.10 The patient may have previously been treated with external beam radiation therapy to other body sites, but not to the target sites.

3.1.11 The patient may have previously or currently be undergoing chemotherapy or bisphosphonate therapy.

3.1.12 The patient will be able to understand English (or a medical interpreter for their native language must be available for all study visits).

3.1.13 18 years of age or older.

3.1.14 Life expectancy > 12 weeks.

3.1.15 Able and willing to answer simple survey questionnaires.

3.1.16 Able and willing to keep a logbook of analgesic use (with or without assistance)

3.1.17 Willing to return to clinic at 4 weeks, 12 weeks, 6 months, and 12 months after treatment.

3.1.18 Signed study-specific informed consent form.

3.1.19 Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.20 The radiation oncologist plans to treat the patient's target lesions with a total of 2-5 fractions of high dose palliative radiation therapy consisting of 5-10 Gy per fraction with a minimum biologic effective dose (BED) of 25 Gy.

3.2 Exclusion Criteria

3.2.1 Inability to lie flat on table for treatment

3.2.2 Patient with ≤ 12 weeks life expectancy

3.2.3 Systemic therapeutic radionuclide delivery within 30 days prior to treatment

3.2.4 Epidural compression of spinal cord or cauda equine

3.2.5 Long bone target lesions must have a Mirels fracture score of ≤ 7

3.2.6 Spinal canal compromise > 25%

3.2.7 Unstable spine requiring surgical stabilization

3.2.8 Target lesions have previously been treated with external beam radiation.

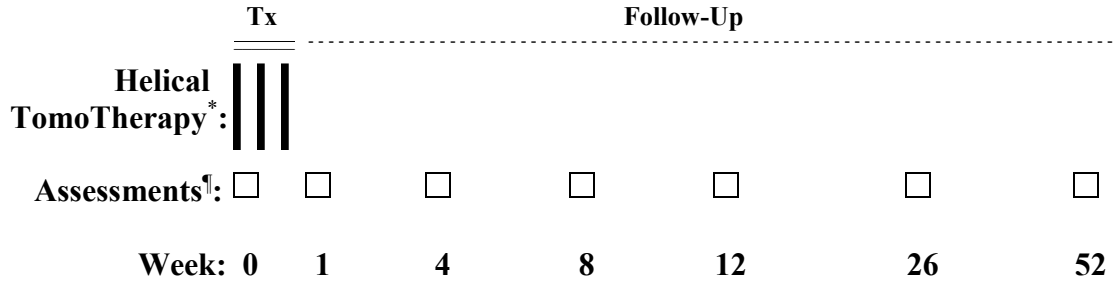
3.2.9 PTV located within 5mm of spinal cord or cauda equina.

3.2.10 A serious uncontrolled medical disorder that, in the opinion of the Investigator, would impair the ability of the patient to receive protocol therapy.

3.2.11 Pregnant and breastfeeding women are excluded from this study.

4.0 TREATMENT PLAN

4.1 Schema



*1-5 helical TomoTherapy radiation treatments over 1-2 weeks
¶ Physical Exam (PE) and/or surveys
Treatment-related toxicity will be captured during treatment PEs and followup PEs.

- This is an investigator-initiated, prospective, non-randomized, multi-centered pilot phase II trial. The clinical trial will be open to accrual at UVA and CRH only.
- We anticipate that it will take approximately 24 months to accrue 30 patients to this pilot study, and each patient will plan to undergo 1 year follow-up.

4.2 Treatment Dosage and Administration: Radiation Therapy

- Approved and consented patients will receive radiotherapy using the STAT RT workflow.
- The patients will receive Helical TomoTherapy using the Hi Art system (TomoTherapy Inc).
- Patients will receive a total of 2-5 fractions of high dose palliative radiation therapy consisting of 5-10 Gy per fraction with a minimum biologic effective dose (BED) of 25 Gy.

- **Dose specifications:** The planning target volume (PTV) will be prescribed a minimum BED of 25 Gy. The maximum dose prescribed will be a BED of 72 Gy.

- **Variations of dose prescription:** There is a wide acceptable range of doses delivered to bone metastases in the palliative setting. The appropriate dose will be determined by tumor histology (whether the tumor is radiosensitive or radioresistant) and location of critical structures (to prevent radiation-induced toxicity to adjacent organs at risk). Dose prescription will be at the discretion of the treating radiation oncologist, however will have to be at least a BED= 25 Gy.

    - **Beam Energy** 6 MV (TomoTherapy only has one beam energy)

    - **Beam Shaping** All treatments will be delivered with conformal delivery with multi-leaf collimator beam modulation.

- **Localization, Simulation and Immobilization:** All patients will undergo non-contrast enhanced kVCT simulations with standard immobilization devices: aquaplast masks for head, neck, upper thoracic PTVs, Vac-Lok cushions or custom headrests, body-fix immobilization system for spinal tumors are all permissible. Diagnostic contrast enhanced CT scans, PET CT scans, or MRIs from the patient's PACS chart will be used to guide target and OAR contouring. The diagnostic images will be rigidly (MRI, contrast enhanced CT, PET CT) or deformably (contrast enhanced CT, PET CT) co-registered to the kVCT simulation in Velocity. Following contour transfer to the kVCT simulation image set, the images will be reviewed and approved by a physician and then transferred to the TomoTherapy treatment planning station.

- An experimental contouring plan will be created to compare to the conventional treatment plan but will not be used in treatment planning. We will experimentally co-register the contoured diagnostic images directly to the MVCT scan and generate the PTV and OAR contours using only the MVCT scan without the kVCT intermediate. Contours generated by both methods will then be compared.

- **Treatment planning/Target Volumes:** Dose will be prescribed to a PTV which will be a gross target volume (GTV) expanded by 0-10 mm depending on critical adjacent structures.

- **Treatment Planning:** TomoHelical (rotational beam delivery) and TomoDirect (fixed beam delivery) techniques in either the IMRT and 3D planning modes are permissible.

- **Critical Structures**

  The following are dose limitations to critical structures. These are accepted dose limitations that have been used in multiple clinical trials of radiotherapy (20, 60).

Table 2: Critical Structures Dose Constraints

Organ	Volume	Total Dose
Spinal cord	Any point	18 Gy maximum
Esophagus	Any point	27 Gy maximum
Ipsilateral brachial plexus	Any point	24 Gy maximum
Heart	Any point	30 Gy maximum
Trachea and ipsilateral bronchus	Any point	30 Gy maximum
Right and left lung	<10% of volume	20Gy or greater
Liver	>700 cc normal liver	<15 Gy
Single kidney	> 66% of volume	<15 Gy
Total Kidney Volume (L+R)	< 35% of volume	≤15 Gy
Stomach	Any point	30 Gy maximum
Bowel	Any point	30 Gy maximum

- **Documentation requirements:** We will provide a dosimetry form that specifies the dosemetric criteria for the PTVs and OARs have been met for each study subject. This will ensure dosimetric compliance with PTV and OAR specifications. The treating radiation oncologist must sign this form for the study to continue.

- **RT Quality Assurance:** Standard quality assurance will be performed with all treatment plans. This involves the placement of a phantom with an array of radiation detecting ion chambers called OmniPro Matrixx on the couch of the TomoTherapy unit. The planned treatment is then delivered to theMatrixx phantom, and the ion chamber array ensures that the correct point dose and geometry is delivered. This ensures that the patient will get the dose as it was planned. Then, while the phantom and then the patient are irradiated, the fluence of the radiation exiting the patient will be measured by the CT detector. The exit dose verification software will then back-project this data collected by the CT detector onto the planning CT scan for volumetric or 3D dose reconstruction. This calculated 3D doses delivered will then be compared to the measured dose recorded by the phantom and also compared to the planned dose.

4.3 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity

according to the Time and Events table (Section 5.1). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0 and the RTOG Late Radiation Morbidity Score (**See Appendix F**).

Radiation Adverse Events

Table 3: Non-hematological Toxicity: Modifications for Recurrent Toxicity

NCI CTCAE Version 4 Grade	Conformal Radiotherapy
0-2	No change from original starting dose
3	Hold until resolved to ≤ Grade 2, then resume treatment.
Second episode of grade 3 or 4 toxicity	Hold until resolved to ≤ Grade 2, then resume treatment.
Third episode of grade 3 or 4 toxicity	Remove subject from trial

Table 4: Non-hematological Toxicities: Modifications for Various Expected Toxicities

Non-hematological Toxicity Dose Reductions for Conformal Radiotherapy	
Event	**Action**
Nausea	
Grade 1-2	None
Grade 3	Hold until resolved to ≤ Grade 2, then resume treatment.
Grade 4	Hold until resolved to ≤ Grade 2, then resume treatment.
Vomiting	
Grade 1-2	None
Grade 3	Hold until resolved to ≤ Grade 2, then resume treatment.
Grade 4	Hold until resolved to ≤ Grade 2, then resume treatment.
Mucositis	
Grade 1-2	None
Grade 3	Hold until resolved to ≤ Grade 2, then resume treatment.
Grade 4	Hold until resolved to ≤ Grade 2, then resume treatment.
Esophagitis	
Grade 1-2	None
Grade 3	Hold until resolved to ≤ Grade 2, then resume treatment.
Grade 4	Hold until resolved to ≤ Grade 2, then resume treatment.
Fatigue	
Grade 1-2	None
Grade 3	Hold until resolved to ≤ Grade 2, then resume treatment.
Grade 4	Hold until resolved to ≤ Grade 2, then resume treatment.
Dermatitis	
Grade 1-2	None
Grade 3	Hold until resolved to ≤ Grade 2, then resume treatment.
Grade 4	Hold until resolved to ≤ Grade 2, then resume treatment.

4.4 Concomitant Medications/Treatments

Not applicable.

4.5 Other Modalities or Procedures

Not applicable.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 2 to 5 fractions depending of the clinical situation. We expect most patients to receive treatments for less than 1 week, however, all treatments will be completed within 21 days. Receiving treatment for > 21 days will be a major protocol violation. Remaining fractions will be discontinued if:

- Inter-current illness that prevent further administration of treatment
- Unacceptable adverse events
- The patient decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.7 Duration of Follow Up

After removal from study, patients will be followed for 12 months after treatment was initiated or until death, whichever occurs first. Patients removed from study for treatment-related adverse events will be followed until resolution or stabilization of the adverse event.

4.8 Pregnancy

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL]. Even women who are using oral, implanted or inject able contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity25 IU/L or equivalent units of HCG, or in accordance with local regulations, whichever is more sensitive) within 7 days prior to the start of study treatment or in accordance with local regulations, whichever is of shorter duration.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

All WOCBP MUST have a negative pregnancy test within 7 days prior to first receiving study treatment. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Male subjects who are actively trying to conceive will be counseled to wait for 6 months following radiation therapy to allow spermatogenesis to recover.

4.9 Removal of Patients from Protocol Therapy

Patients will be removed from study when any of the criteria listed in Section 4.6 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.10 Expected Adverse Events

Depending on the site of treatment, potential / expected treatment toxicities include Grade 1 to 3 toxicity of the following symptoms, with Grade 3 occurring in no more than the following percentages of patients:

Dermatitis	20%
Nausea	20%
Fatigue	20%
Vomiting	20%
Diarrhea	20%
Mucositis	20%
Esophagitis	20%

5.0 EVALUATIONS AND ASSESSMENTS

5.1 Time and Events Table

	Pre-treatment	During treatment	Week 1	Week 4	Week 8	Week 12	6-Month	12-Month
Informed Consent	X							
History and PE	X			X		X	X	X
Karnofsky Performance Status	X		X	X	X	X	X	X
Toxicity Evaluations		X	X	X	X	X	X	X
Opiod Logbook Evaluation	X	X	X	X	X	X		
Brief Pain Inventory	X		X	X	X	X	X	X
FACT-BP and FACT-G surveys	X		X	X	X	X	X	X
Satisfaction and Convenience Survey	X		X	X	X	X	X	X
Quality Assurance	X							
Diagnostic Imaging (CT/MRI/PET CT)	X							
Pathology	X							
Pregnancy test (≤ 7 days)	X							
Radiotherapy Delivery		X						
Exit Radiation Dose Verification		X						
Intrafractional Motion Monitoring		X						
Conventional and Expedited Image Registration Flow		X						

5.2 Correlative Studies Procedures

Not applicable.

5.3 Final Study Visit

The final study visit will occur at the 12 month visit. See the Time and Events Table for assessments that will be performed. Patients removed from study for treatment-related adverse events will be followed until resolution or stabilization of the adverse event

5.4 Early Termination Visit

Subjects may withdraw voluntarily from participation in the study at any time. At the time of withdrawal, the subject will be requested to provide their opioid logbook and complete the following surveys: BPI, FACT-BP/FACT-G, and Satisfaction survey.

Subjects may also withdraw voluntarily from receiving the study intervention for any reason. If that is the case, they will be encouraged to continue regular follow-up evaluations according to the Time and Events table.

As all of these patients have metastatic cancer and a limited life expectancy, it is likely that a reasonable percentage of study participants will choose hospice care before the completion of their follow-up.

6.0 EVALUATION CRITERIA

6.1 Response to Palliative Radiotherapy

6.1.1 Response Criteria According to the International Bone Metastases Consensus Group

Complete Response (CR):	Pain reduction to zero AND OMED* stable or reduced
Partial Response (PR):	Pain reduction by two scores or more AND OMED* stable or reduced. OR Stable pain AND OMED* reduction by 25% or more
Pain Progression (PP):	Pain increase by two scores or more AND OMED* stable or increased. OR No change in pain AND OMED* increased by 25% or more (or start of morphine use after the baseline or epidural pain treatment at follow-up)
Stable Pain (SP):	Stable pain AND stable OMED*

OMED = Oral Morphine Equivalent Dose
* The total OMED intake over the most recent 72 hours will be calculated at each evaluation.

6.1.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for Complete Response or Partial Response (whichever is first recorded) until the first date that Stable Pain or Pain Progression is objectively documented.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that Partial Response is objectively documented.

Duration of stable pain: Stable Pain is measured from the start of the treatment until the criteria for Pain Progression are met, taking as reference the baseline measurements recorded just prior to treatment.

6.1.3 Response Review

The endpoints in this study are all quantitative based on validated surveys and pain scores that are reported by the patients. Thus, we do not feel that a review by an expert independent of the study is necessary or valuable.

6.2 Toxicity and Safety

All patients who receive treatment on this protocol will be evaluable for toxicity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4 and the RTOG Late Radiation Morbidity Scoring Criteria at time points indicated in the Time and Events table in Section 5.1.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design

This is an investigator-initiated, prospective, non-randomized, single-centered phase II clinical trial. This clinical trial will have a primary aim of determining outcomes of patients treated with a conformal hypofractionated STAT RT treatment utilizing widely accepted surveys and questionnaires and clinical examinations. The secondary aim is to collect clinical data to optimize software integration to develop the Scan-Plan-Treat STAT RT workflow that will make the entire process much quicker and efficient for the patient and clinic. The University of Virginia diagnoses almost 3000 cancers annually and we treat

approximately 80 patients with osseous metastases each year in the Department of Radiation Oncology. We anticipate it will take approximately 18 months to accrue 30 patients to this pilot study.

1) Primary Aim: Evaluation of Outcomes of Patients with Osseous Metastases Treated with STAT RT

We will recruit 30 cancer patients with 1-3 painful osseous metastatic lesions (target sites) requiring opioid medication who are candidates for palliative radiation therapy. Patients will receive 2-5 fractions of 5-10 Gy (minimum BED of 25 Gy) of conformal radiation therapy delivered to the target sites via the Helical TomoTherapy system using the STAT RT workflow. Patient pain, analgesic use, function, quality of life, and satisfaction will be recorded prior to treatment, at 1 week, 4 weeks, 8 weeks, 12 weeks, 6 months, and 12 months after therapy using the following measures:

a) The Brief Pain Inventory (BPI)
b) Patients will keep an analgesic use logbook and have their doses converted into Oral Morphine Equivalent Doses (OMED).
c) Treatment response will be measured by the guidelines set forth by the International Bone Metastases Consensus Group as described in Section 6.1.1.
d) The FACT-BP and FACT-G questionnaires
e) Karnofsky Performance Scale (KPS)
f) Patient Satisfaction will be measured by a modified FACIT-TS-BTCSQ survey.

Radiation-induced treatment related toxicities will be captured during treatment and at the above time points and graded using the CTCAE Version 4.0 and the RTOG Late Radiation Morbidity Score Criteria.

2) Secondary Aim: Optimization of Software Integration for Scan-Plan-Treat Workflow

Several secondary investigational aims will be studied that will not be used in direct patient care but are essential in further streamlining the STAT RT workflow. These components will not subject the patient to any additional inconvenience or risk. Standard patient-specific quality assurance will be performed on a Matrixx ion chamber array.

a) Optimization of Novel Image Co-registration Workflow

The standard two step image co-registration process of contoured diagnostic images to kVCT simulation scans and then kVCT simulation scans to MVCT image guidance scans will be used to treat all patients. We will then experimentally co-register the contoured diagnostic images directly to the MVCT scan, and the PTV and OAR contours generated onto the MVCT scan by both methods will then be compared.

To evaluate the conventional and the experimental image registration flows, the two registration flows will be compared in the following manner:

- Gross tumor volumes (GTVs) will be generated from both the conventional and experimental image registration flows. The differences in volume and the distances between the two centers of the GTVs will used to evaluate the similarity of the two GTV contours.
- Spinal cord contours will also be generated from both registration flows. The point of the spinal cord that has the shortest distance to the center of the GTV will be identified for each contour. The distance between the points from the two registration flows will be used to evaluate the similarity of the two cord contours. The volumes of the two cords will also be compared.
- Quantitative evaluation of the contours will be performed using the Dice index. Dice index is defined as the overlapping volume of two structures divided by the average volume of the two. Clearly, Dice index is 1 if the two structures are identical and 0 if they do not share any voxel. Dice index will be calculated in Velocity for contours generated on conventional and experimental image registration flows. Dice indices of 0.8 or higher are acceptable based on literature (61).

b) Treatment Planning Speeds

We will determine the speed of radiation treatment planning with our current clinical system and compare this to the speed of planning with newer in-development algorithms running on next generation computers with graphic processing units (GPUs). Since highly conformal radiation treatments must be routinely calculated in a few minutes for the Scan-Plan-Treat STAT RT workflow, we will determine if the treatment planning with GPUs is fast enough for clinical implementation (i.e. can be done in approximately 5 minutes). If not, we will optimize the planning process in collaboration with TomoTherapy, Inc to increase the speed of planning.

c) Exit Radiation Dose Verification

In-development software provided by TomoTherapy Inc.® will be used to measure the exit dose fluence, backproject this fluence as entrance fluence, and then calculate the patient dose on the MVCT scan. This software will be further optimized and refined on this clinical trial. All patients' radiation treatment plans will undergo standard of care phantom-based quality assurance measurements. The phantom exit dose will also be calculated via this software in this optimization process. By comparing the values obtained with the software to the calculated treatment plan and phantom measurements, we hope to optimize this novel radiation dose verification software to +/- 3% calculated to delivered dose. Preliminary data shows that we are already at +/- 5% calculated to delivered dose (53).

d) Infrared Motion Tracking System (UVA patients only)

An in-house developed infrared motion tracking system will be optimized at the Emily Couric Cancer Center. The system will initially be validated on 10

healthy volunteers who will be instructed to lie still on the couch for 10 minutes. Following that, a small couch motion of 1-5 mm will be introduced in the x, y and z directions and compared with the motion detected by the infrared cameras. After the system is validated with the healthy volunteers, it will then be used to monitor the intra-fractional motion of patients treated on this protocol during treatment. We anticipate having to modify/edit the software code during clinical implementation.

All patients undergoing treatment at UVA will have "set up" skin marks placed as is standard of care for laser alignment of the patient prior to MVCT scan image guidance, which is then used for finer (generally millimeter) adjustments of internal target volumes. Following scanning we will note the position of the lasers with respect to the set up skin marks, and at the completion of treatment we will again measure the location of the set up marks to the lasers. With this data we can determine if the patient had moved after the image guidance MVCT or during treatment, and we will compare this with data from the infrared tracking system. This system does not utilize ionizing radiation, add additional burdens or constraints, cause any discomfort or side effects, and is completely noninvasive. In reality, an additional layer of safety is added to the STAT RT treatment as any unexpected patient motion will be monitored and reported. We anticipate that this system will be able to accurately track patients with +/- 2-3 mm of motion accurately.

Stopping Rules:

The study will be suspended for a safety review if 5 or greater "Probable" or "Definite" Serious Adverse Events occur or greater than 5 unexpected toxicities of $\geq$ Grade 3 occur.

7.2 Sample Size and Accrual

We performed calculations to detect a change in patients' BPI pain scores before and after treatment using the Wilcoxon signed-rank test. Using the software G*Power 3.1.2 (University Kiel, Germany) the following calculations were made. To detect a mean change of 2 units on the BPI scale with a standard deviation of 3, and achieve a 2-sided alpha of 0.05 with 80% power, a sample size of 21 is needed. Most studies report a mean improvement in pain scores of about 3.5. (32). Thus we anticipate an improvement by at least 3 on the BPI in our study, which should be adequately powered with 30 patients.

Since we have had accrual from prior studies of about 20 patients a year and this is a pilot study, we thought that a sample size of 30 subjects would be realistic for accrual and provide the necessary patient data for optimization of the software systems. We treat approximately 30 patients with osseous metastases annually at UVA with palliative radiotherapy. We anticipate an accrual rate of 20 cases per year over 18 months. Since the power analysis requires a sample size of

21, accrual of 30 subjects would allow for dropouts and still have sufficient power.

7.3 Data Analyses Plans

Treatment response as defined by International Bone Metastases Consensus Group will be determined for each patient. As described in Section 6.1.1, pain intensity as defined by the BPI and opiate use as quantified by the OMED will be used to categorize patients as having: Complete Response, Partial Response, Pain Progression, Stable Pain. At each evaluation, the patient's BPI and OMED at that visit will be compared to the pre-treatment levels. The "Worst Pain" score from the patient's BPI will be used to evaluate for treatment response. Patient response does not require a statistical analysis. The percentage of patients in each response category at each evaluation will be reported.

Patient pain will be recorded using the BPI before treatment and at designated evaluations after treatment. Pain scores before and after treatment will be compared using a Wilcoxon signed ranks test to determine if there is a statistically significant difference. Example: Pre-treatment vs. 1 week, Pre-treatment vs. 4 weeks, etc.

Analgesic use will be recorded by requiring each patient to keep a logbook of their analgesic intake. Their opiate intake for the last 72 hours will be converted to OMED at each evaluation and used in the categorization of treatment response. The difference between their OMED before and after treatment will be compared using paired two-sample t-tests.

Patients' functional status will be determined using the Karnofsky Performance Scale at each evaluation. The difference between the KPS before and after treatment will be compared using a Wilcoxon signed ranks test.

Patients' quality of life will be measured using FACT-BP and FACT-G scores at each evaluation. The difference between the FACT scores before and after treatment will be compared using a Wilcoxon signed ranks test.

Patient satisfaction will be measured using a modified version of FACT - TS – BTCSQ. No statistical analysis will be required for reporting the results. The average scores from the satisfaction survey will be reported.

To evaluate the CT detector dose calculations, the delivered radiation dose obtained using the phantom quality assurance will be compared to the exit radiation dose quality assurance calculation. The calculated dose and delivered dose for each patient will be compared using a paired two-sample t-test, and the % difference in dose will be reported.

Contours generated from the conventional and experimental image registration flows will be compared in a variety of ways as described in Section 7.1. All comparisons of the contouring measures, including the Dice indices, will be performed using paired two-sample t-tests.

Toxicity will be recorded using CTCAE 4.0 criteria and RTOG Late Radiation Morbidity Scoring Criteria. The incidences of grade 3 or more toxicities will be reported.

The effectiveness of the infrared tracking system will be determined by comparing its position calculations with the position of the patient as determined by the position of the lasers with respect to the set up skin marks before and after treatment. The position changes calculated by each method will be compared using paired two-sample t-tests.

The average treatment planning speed of radiation treatment planning with our current clinical system will be calculated and compared the average speed of planning with newer in-development algorithms running on next generation computers with graphic processing units. These means will be compared with two-sample t-tests.

8.0 ADVERSE EVENTS AND REPORTING

The treating physician is required to notify the UVA Data Safety Monitoring Board (DSMB), and the UVA Institutional Review Board (IRB-HSR) of any of any serious adverse event (SAE).

8.1 Definition

8.1.1 Adverse Event

An adverse event is any undesirable medical experience occurring to a subject who has been given an investigational product, whether or not related to the study treatment(s). Medical conditions present before starting the investigational treatment/intervention will be considered adverse events only if they worsen after starting study treatment. The following are adverse events:

- All unfavorable, harmful or pathological changes in the general condition of a patient.
- Subjective or objective symptoms (spontaneously offered by the patient and/or observed by the Investigator or the study nurse).
- All intercurrent events or exacerbation of pre-existing diseases which occurred after the administration of the study treatment.
- All clinically significant changes in laboratory abnormalities.

- Any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious (see below, definition of SAE). This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. AEs will be collected up to 30 days post last dose of study treatment in all cases including early study termination. If an ongoing AE changes in its severity or in its perceived relationship to study treatment, a new AE entry for the event should be completed.

8.1.2 Unexpected Adverse Event

An unexpected adverse event is any adverse treatment experience where the specificity or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

8.1.3 Serious Adverse Event

A serious adverse event or experience (SAE) or serious adverse drug reaction (ADR) is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant disability/incapacity;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis

interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

8.2 Attribution Assessment

The Principal Investigator will evaluate all AEs and assess their toxicity and attribution, if any, to study treatment. The following criteria will define the attribution:

Definite: The AE is clearly relation to the investigational agent.
Probable: The AE is likely related to the investigational agent.
Possible: The AE may be related to the investigational agent.
Unlikely*:* The AE is doubtfully related to the investigational agent.
Unrelated*:* The AE is NOT related to the investigational agent.

8.3 Serious or Unexpected Adverse Event Reporting Requirements

This section may need revision if Sponsor or Funding Source of study has specific reporting requirements for trial, and/or if study is conducted under an IND.

For any serious or unexpected event which occurs to any patient in the course of their treatment on this study or within 30 days following cessation of treatment, the UVA Study Coordinator must inform:

- **The Principal Investigator verbally within 24 hours.**
- **Written report to the UVA Office of Clinical Research, DSMC, and IRB within 7 days.**

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

8.4 UVA Cancer Center DSMC AE Reporting Requirements

All adverse events will be recorded on appropriate case report forms. In addition, AE Reporting will occur via the UVA Cancer Center clinical trials reporting system, C3TO (TABLE Below).

Therapeutic Medium Risk Phase II Studies
Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment

	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected	Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	C3TO 30 days	C3TO 15 days	C3TO 30 days	C3TO 15 days	C3TO 15 days	C3TO 15 days
Possible Probable	C3TO 30 days	C3TO 30 days	C3TO 15 days	C3TO 30 days	C3TO 15 days	C3TO 15 days	C3TO 15 days	C3TO 15 days	C3TO (24-hrs)*

Definite									7 days

*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment
Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

8.5 UVA IRB Reporting Requirements

Reporting to the UVA HSR-IRB will follow the institutional plan as outlined in the table below. In addition, DSMC reports will be furnished to the IRB within 15 calendar days of study team's receipt of report.

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation (Note: An internal event is one that occurs in a subject enrolled in a UVa protocol.)	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event Only for events as outlined in section 8.0.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations (Note the IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.) Or Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html*

Data Breach	The UVa Corporate Compliance and Privacy Office	As soon as possible and no later than 24 hours from the time the incident is identified.	UVa Corporate Compliance and Privacy Office: Phone 924-9741
	ITC: If breach involves electronic data.	As soon as possible and no later than 24 hours from the time the incident is identified.	ITC: Information Security Incident Reporting Procedure, http://www.itc.virginia.edu/security/reporting.html
	UVa Police if breach incluces such things as stolen computers.	IMMEDIATELY	Phone – (434) 924-7166

9.0 DATA SAFETY MONITORING PLAN

The Principle Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the UVA Data Safety Monitoring Committee (DSMC).

9.1 Internal (Investigator) Study Monitoring Plan

The University of Virginia Data Safety Monitoring Committee (DSMC) requires the Principal Investigator to review all patient data at least monthly and to provide a semi-annual report. Review of adverse events assessment will be performed by the Principal Investigator with study personnel. Minutes of these meetings will be maintained and provided to the DSMC with the semiannual review. At these meetings the following will be discussed:

- Participant safety (AE reporting)
- Data validity, integrity, and completeness
- Enrollment and retention
- Protocol adherence

In addition, the DSMC requires semi-annual auditing by the Vice President of Research and Graduate Studies (VPRGS) compliance monitors. The VPGRS monitor's semi-annual audit will be reviewed by the Principal Investigator and the DSMC Chair

9.2 UVA Cancer Center Data Safety Monitoring Committee

The University of Virginia Cancer Center Data and Safety Monitoring Committee (DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC).

The DSMC will review the following:

- All adverse events
- Audit results

- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

The CC DSMC will meet every month for aggregate review of AE data. Tracking reports of the meetings are available to the PI for review. Issues of immediate concern by the DSMC are brought to the attention of the PI (and if appropriate to the PRC and IRB) and a formal response from the PI is requested. Per the Cancer Center NIH approved institutional plan this study will be audited approximately every 6 months.

10.0 STUDY MANAGEMENT

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.2 Registration Procedures

All patients must be registered with the C3TO at the University of Virginia Cancer Center before enrollment to study.

10.3 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.3.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB-HSR approval/favorable opinion.

For any such emergency modification implemented, a UVA IRB modification form must be completed by study Personnel within five (5) business days of making the change.

10.3.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

10.3.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB.

Protocol Deviations: A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

CRC of record will record the deviation, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Violations should be reported by CRC of record to the IRB within one (1) week of the investigator becoming aware of the event.

10.4 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.5 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

APPENDIX A

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4

An electronic copy of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 can be obtained from the World Wide Web CTEP site. The web address is:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX B

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

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

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*	0	1	2	3	4
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

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

FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I am able to work (include work at home)	0	1	2	3	4
My work (include work at home) is fulfilling	0	1	2	3	4

I am able to enjoy life	0	1	2	3	4
I have accepted my illness	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun	0	1	2	3	4
I am content with the quality of my life right now	0	1	2	3	4

APPENDIX C

FACT-BP
QUALITY OF LIFE MEASUREMENT IN PATIENTS WITH BONE PAIN

Please answer the following questions about your bone pain. Sometimes it is not easy to tell whether a pain you might have is bone pain or some other type of pain. Please do the best you can to answer these questions about your bone pain in particular. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

In how many places in your body have you felt bone pain?	0	1	2	3	4+

	Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I am content with the quality of my life right now……	0	1	2	3	4
I have certain parts of my body where I experience significant pain……...	0	1	2	3	4
I have bone pain…….	0	1	2	3	4
It hurts when I put weight or pressure on the place where I have bone pain.....	0	1	2	3	4
I have bone pain even when I sit or lie still.....	0	1	2	3	4
I need help doing my usual activities because of bone pain	0	1	2	3	4
I am forced to rest during the day because of bone pain	0	1	2	3	4
I have trouble walking because of bone pain…….	0	1	2	3	4
Bone pain interferes with my ability to care for myself (bathing, dressing, eating, etc.).....	0	1	2	3	4
Bone pain interferes with my social activities……..	0	1	2	3	4

Bone pain wakes me up at night……..	0	1	2	3	4
I am frustrated by my bone pain	0	1	2	3	4
I feel depressed about my bone pain.....	0	1	2	3	4
I worry that my bone pain will get worse…….	0	1	2	3	4
My family has trouble understanding when my bone pain interferes with my activity	0	1	2	3	4

APPENDIX D

Bone Treatment Convenience and Satisfaction Questionnaire
FACIT-TS-BTCSQ – Baseline (Modified)

For each statement, please choose the response that best describes your expectation of this treatment.

"Treatment for bone disease" means the radiation you receive to treat your bone disease only, NOT your other cancer treatments.

Treatment for Bone Disease Expectations	**Not at All**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I believe that my treatment for bone disease will cause me physical pain	0	1	2	3	4
I believe that receiving treatment for bone disease will be inconvenient.	0	1	2	3	4
I worry that my treatment for bone disease will not be effective.	0	1	2	3	4
I believe that treatment for bone disease will be harmful to me.	0	1	2	3	4
I believe that my treatment schedule for bone disease will be <u>stressful to me</u>.	0	1	2	3	4
I believe that my treatment schedule for bone disease will be <u>stressful to my family</u>.....	0	1	2	3	4
I believe that I will be bothered by side effects of treatment for bone disease	0	1	2	3	4

APPENDIX E

Bone Treatment Convenience and Satisfaction Questionnaire
FACIT-TS-BTCSQ – On Treatment (Modified)

The following to be completed by patient.

The following is a list of statements that people receiving bisphosphonate therapy have commented are important. For each statement, please choose the response that best describes your expectation of this treatment.

"***Treatment for bone disease***" means the drug(s) you receive to treat your bone disease only, **NOT** your other cancer treatments.

Treatment for Bone Disease Expectations	**Not at All**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Treatment for bone disease takes up my time	0	1	2	3	4
My treatment for bone disease takes up my family's time.....	0	1	2	3	4
I worry about side effects from treatment for bone disease.....	0	1	2	3	4
My treatment for bone pain causes me physical pain	0	1	2	3	4
Receiving treatment for bone disease is inconvenient.	0	1	2	3	4
I worry that my treatment for bone disease will not be effective.	0	1	2	3	4

Treatment for bone disease seems harmful to me.	0	1	2	3	4
My treatment schedule for bone disease is stressful to me.	0	1	2	3	4
My treatment schedule for bone disease is stressful to my family	0	1	2	3	4
I am bothered by side effects of treatment for bone disease. ……	0	1	2	3	4

Considering your experience with treatment for bone disease to date, please respond to the following questions.

	No, not at all	**Yes, to some extent**	**Yes, for the most part**	**Yes, completely**
Are you satisfied with the results of the treatment for your bone disease so far?	0	1	2	3

	No	**Maybe**	**Yes**
Would you recommend this treatment for bone disease to others with your illness?.....	0	1	2
Would you choose this treatment for bone disease again?	0	1	2

Time Used for Hospitalizations and Outpatient Medical Visits

1) How many times and for how long did you have a hospital stay or an outpatient visit during the past 4 weeks?
(Please complete the table below.)

	Total Number of Visits	Average Length of Visit	
Hospital Admissions			days
Family Practice Visits			hours
Specialist Visits			hours
Emergency Visits			hours
Other Visits			hours

2) We would like to know the cost incurred by you or by someone helping you with transportation to and from the above visits during the past 4 weeks.
(Please complete the table below.)

	Total Number of Trips	Average Kilometers per Trip	Average Time of Trip				Average Cost
Ambulance				hours		mins	
Private Vehicle				hours		mins	
Public Transport/Taxi				hours		mins	

3) During the past 4 weeks, how much total time did you or someone helping you miss from work or leisure time due to actual visits and travel time? (Please complete the table below)

Time Missed from Work/Leisure	**Days**	**Hours**
Total time missed by patient		
Total time missed by someone helping patient		

APPENDIX F

RTOG Late Radiation Morbidity Scoring Table

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION LATE EFFECTS
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness of mouth Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/ Blindness	
LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest)	Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low ORS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required	Necrosis/ Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula	
LIVER	None	Mild lassitude Nausea, dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis/ Hepatic coma or encephalopathy	
KIDNEY	None	Transient albuminuria	Persistent moderate	Severe albuminuria	Malignant	

		No hypertension Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75%	albuminuria (2+) Mild hypertension No related anemia Moderate impairment of renal function Urea>36-60 mg% Creatinine clearance (50-74%)	Severe hypertension Persistent anemia (<10g%) Severe renal failure Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance <50%	hypertension Uremic coma/Urea >100%	
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/ Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/ Complete fixation	

APPENDIX G

Mirels Fracture Score

Variable Score	1	2	3
Pain	Mild	Moderate	Severe
Location	Upper Extremity	Lower Extremity	Peritrochanteric
Size*	Less than 1/3	1/3 to 2/3	Greater than 2/3
Nature	Blastic	Mixed	Lytic

*Size = The degree of cortex taken up by the lesion (<1/3, 1/3-2/3, >1/3)

APPENDIX H
Brief Pain Inventory

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

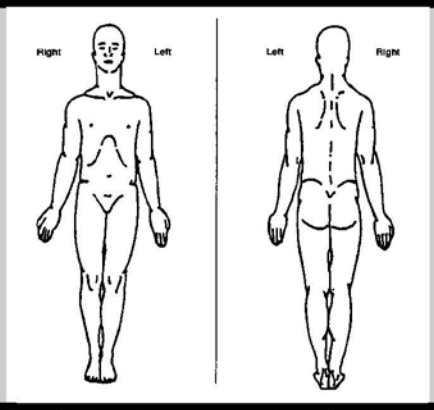
Name: _____ _____ _____

Last First Middlle Initial

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

   1. Yes 2. No

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



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

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

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

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

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

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

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

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

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

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

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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