University of Arizona
Medical University of South Carolina

Protocol
Phase 2 Study of Vertebral Augmentation and Radiotherapy in Painful or at Risk of Collapse Spinal Metastatic Cancer/Multiple Myeloma

Principal Investigator
Krisha Howell, MD
Department of Radiation Oncology
University of Arizona
Phone: (520) 694-8961
Email: KrishaHowell@email.arizona.edu

Neurosurgery Co-Investigators
Ali Baaj, MD
PO Box 245070
1501 N. Campbell Ave.
Tucson, AZ 85724
Phone: (520) 626-2164
Email: abaaj@surgery.arizona.edu

Radiation Oncology Co-Investigators
Baldassarre Stea, MD, PhD
1501 North Campbell Ave
Tucson, AZ 85724
Phone: (520) 694-7236
Email: bstea@email.arizona.edu

David T. Marshall, MS, MD
Department of Radiation Oncology
Medical University of South Carolina
169 Ashley Avenue
Charleston, SC 29425
Phone: (843) 792-3271
Email: marshadt@musc.edu

Statistician Co-Investigator
Elizabeth Garrett-Mayer, PhD
Medical University of South Carolina
86 Jonathon Lucas St, Room HO118G
Charleston, SC 29425
Phone: 843-792-7764
Email: garrettm@musc.edu

Protocol Approved: 8-20-2013
Revised 9-9-2013
Revised 3-6-2014
Revised 3-19-2014
Revised 7-16-2014
Revised 3-11-2015

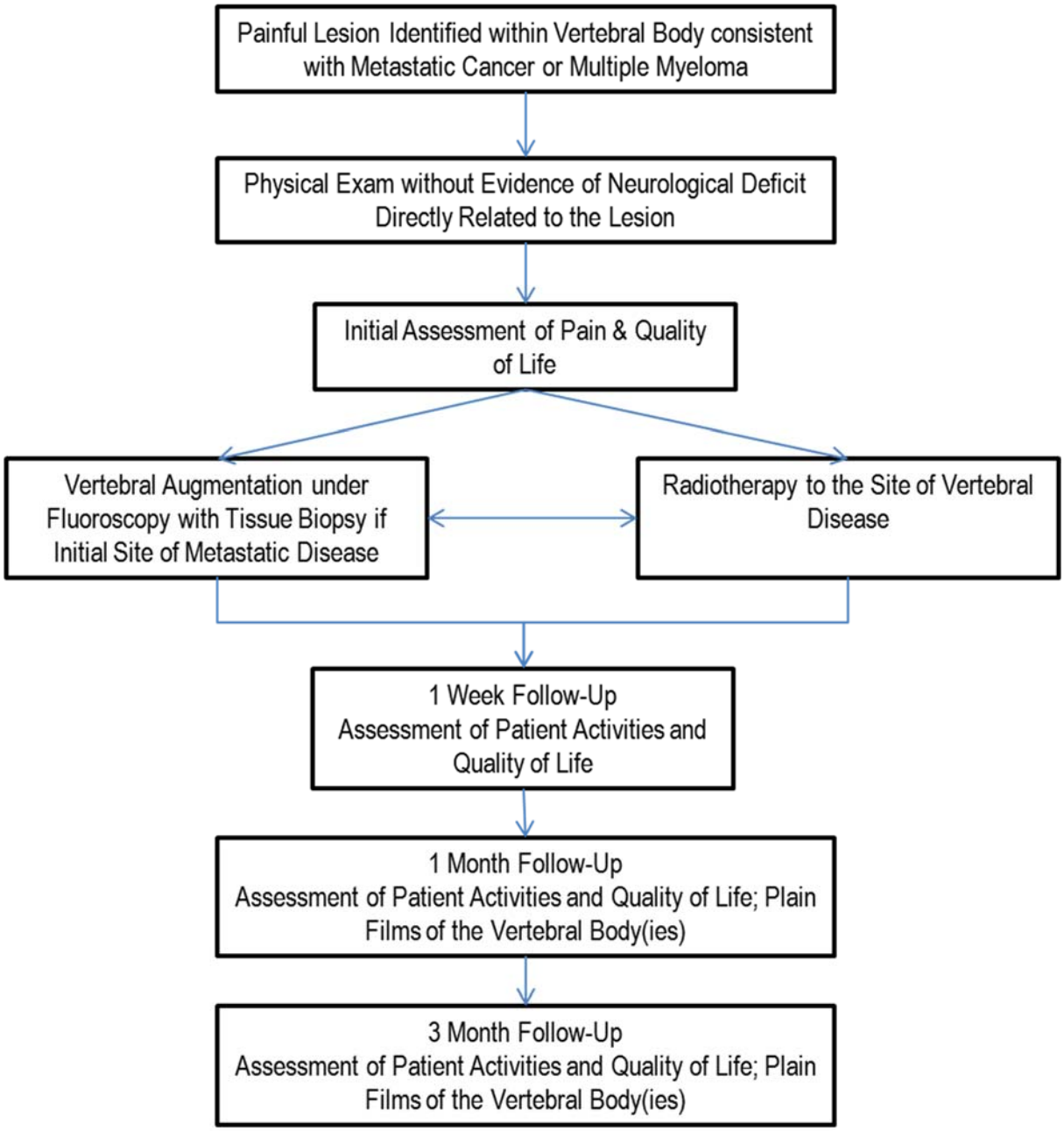
Table of Contents

Appendices

Appendix I	- Worst Pain Assessment on the Brief Pain Inventory Scale
Appendix II	- Roland-Morris Disability Questionnaire
Appendix III	- EORTC QLQ-C30 (version 3)
Appendix IV	- Pain Measures Index and Narcotic Score
Appendix V	- Baseline Data Collection Form
Appendix VI	- Follow-up Report
Appendix VII	- Karnofsky Performance Status
Appendix VIII	- Record of Current Pain Medications
Appendix IX	- Study Parameter Table

Phase 2 Study of Vertebral Augmentation and Radiotherapy in Painful or at Risk of Collapse Spinal Metastatic Cancer/Multiple Myeloma

SCHEMA



Patient Population: (See Section 3.1 for Eligibility)
Adults with a suspicion of metastatic cancer to the vertebrae or multiple myeloma with a focus in a vertebral body(ies). The lesion must be identifiable with radiologic evidence and the diagnosis of metastatic disease fulfilled.

Required Sample Size: 20 patients (with a Pain Scale Score of equal to or greater than 5)

ELIGIBILITY CHECKLIST

Inclusion Criteria

_____ (Y) 1. Does the participant have a suspicion of metastatic cancer to the vertebrae or multiple myeloma with a focus in a vertebral body(ies) per section 3.1? Type of cancer: _____

_____ (Y) 2. Has a history and physical exam been done within 8 weeks prior to registration? Date: ___/___/_____

_____ (Y) 3. Has a lesion(s) been identified on X-ray, bone scan, CT scan or MRI? Type of Scan: _____ Date: ___./___/_____

_____ (Y) 4. Is the participant 18 or older? Age: ____ Date of Birth: ___/___/_____

_____ (Y/NA) 5. Is the participant female and of childbearing potential?

If yes, has a pregnancy test (urine dipstick or serum) been negative within 2 weeks prior to registration?

_____ (Y) 6. Is the participant's Karnofsky performance status $\geq$ 40? Score: ____

_____ (Y/NA) 7. If the participant has childbearing potential, has she/he agreed to practice an adequate mean of birth control throughout treatment in this study and for 6 months after his/her last treatment?

_____ (Y) 8. Are there indications for intervention per section 3.1?

Either pain with a focus at the involved vertebral body that is not adequately controlled by medical management **or** Osteolysis of a vertebral body(ies), with pain, with or without fracture at a site of metastatic infiltration/multiple myeloma that poses a risk of impending vertebral collapse?
Pain Level:_____ (Must be 5 or greater)

_____ (Y) 9. Written informed consent completed. Date: ___/___/_____

_____ (Y) 10. The participant is fully able to understand the English language so as to read and answer the study questionnaires.

_____ (Y) 11. The participant has the absence of any serious cognitive or psychiatric problems that could potentially hamper compliance with the study and follow-up schedule.

_____ (Y) 12.Is the participant's pain scale score $\geq$ 5?

_____ (Y) 13. Diagnostic imaging to be obtained at time of kyphoplasty if not previously done.

Exclusion Criteria

_____ (N) 14. Does the participant have spinal cord compression?

_____ (N) 15.Is the participant currently using Plavix or has a history of taking Plavix less than 7 days prior to enrollment?

_____ (N) 16.Is there evidence of a local infection at the puncture site or evidence of a systemic infection?

_____ (N) 17.Does the participant have a known allergy to any of the components used during vertebral augmentation?

_____ (N) 18.Does the participant have a co-morbidity that would cause cardiorespiratory compromise during conscious sedation or in the prone decubitus position?

_____ (N) 19.Does the participant have a life expectancy of less than 3 months? Documentation based on? Low Clinical morbidity? YES NO Other_____

_____ (N) 20. Previous radiotherapy to the current vertebral body(ies) with metastatic disease currently under consideration for treatment.

_____ (N) 21. Patient has participated in this study before.

_____ (N) 22. Patient was treated Samarium therapy or SM153, or lexidronam, or other hormone.

_____ (N) 23 . Patient has asymptomatic vertebral fracture and is at low risk for biomechanical instability and collapse.

_____ (N) 24. Patient has a known allergy to any of the components used during vertebroplasty (PMMA bone cement)

_____ (N) 25. Patient's pain is not localized to the region of metastatic disease. This may include diffuse non-focal back pain and/or Radiculopathy.

1.0 INTRODUCTION

The following study aims to gain a rapid improvement in the patient's functional status and quality of life in patients with vertebral body metastases by decreasing the associated pain, and preventing further vertebral fracture, loss of height, and instability. Furthermore, this study aims to prevent further cancerous disease progression, reduce pain and bony destruction to the affected vertebral bodies. This will be accomplished by combining vertebral augmentation (VA) and radiotherapy.

The proposed study seeks to evaluate and quantify the reduction of pain and changes in quality of life in relevance to vertebral augmentation in addition to radiation therapy. This study will be conducted in those patients with metastatic cancer or multiple myeloma involving the vertebral body(ies). Although there are extensive studies on vertebral augmentation in the setting of osteoporotic spinal fractures, there are few in the setting of metastatic disease. Those studies that do exist either do not account for possible radiation or were not performed in a prospective manner with adequate follow-up. This study aims to address the value of vertebral augmentation in combination with radiotherapy in the setting of cancer to the spine. The proposed study will be the first that we are aware of with the capability to assess patient response to vertebroplasty and radiotherapy with a scale and time interval comparable to the historical controls treated with other approaches. Thus, the patient's pain, overall quality of life, and fracture development/avoidance will be assessed at set time intervals to determine the change from historical controls treating patients with radiotherapy only.

1.1 Bone Metastasis and Radiotherapy

In the setting of metastatic lesions to the spine, laminectomy and surgical stabilization are common techniques for areas of symptomatic disease threatening instability. Radiotherapy treats the underlying cancer, attempting local control of the disease but, during the immediate time period following radiation, may leave the bone in a weakened state. In such a state there can be a risk of fracture until the bone can be remodeled as it heals. As exemplified by the Radiation Therapy Oncology Group (RTOG) 7402 trial of external beam radiation for bone metastases, maximal pain relief develops over the course of weeks from the time of completion of radiation. It may take up to 20 weeks to express the full effects of pain control.[1] RTOG 7402 was a randomized control trial of patients with solitary or multiple metastases in the femur, humerus, pelvis, or spine. The patients exhibited a pain or narcotic score of at least 4 and an expected survival of at least 3 months. Patients were stratified based on their number of bone metastases into one of 2 or one of 4 different dose fractionation schedules. Between the fractionation schedules, there was no difference in pain relief or relapse from pain relief. Close to 50% of patients who had complete relief, first reported it more than 4-weeks after completing treatment. Unfortunately, relapse of the pain occurred in 29% of patients having experienced minimal pain relief, 41% of patients having had partial pain relief, and 54% in patients having had complete pain relief.

Following RTOG 7402, RTOG 9714 was conducted to assess varying the fraction regimen for metastatic disease. In this trial, 949 patients with prostate or breast cancer and painful bone metastases were treated with 8 Gy in a single fraction or 30 Gy in 10 fractions. There were no significant differences in the rates for complete and partial pain relief, the use of narcotics, and/or the incidence of subsequent pathologic fractures. Patients treated with a single fraction were twice as likely to be retreated (18% vs 9%), which may be related to the convenience of a one time treatment and the comfort level of radiation oncologists with retreating after 8 Gy versus 30 Gy.[2] Radiation fractionation schedules currently in use at our institution closely parallel those assessed in both RTOG 7402 and RTOG 9714: 30Gy in 10 fractions, 20Gy in 5 fractions, or 8Gy in 1 fraction.

1.2 Vertebral Augmentation

Vertebroplasty was developed in 1987 in France for percutaneous treatment of a fractured vertebral body. In this procedure the clinician uses a large-bore needle to access a fractured vertebral body percutaneously, under imaging guidance (fluoroscopy and/or computer assisted tomography (CT)), and inject bone cement, generally using conscious sedation. Thereby, the vertebral body is stabilized and the bony structure reinforced.[3] Kyphoplasty is the same procedure as vertebroplasty, but before injecting the cement in the vertebral body, a balloon is inflated in the vertebral body in order to create a chamber that should allow one to inject the cement at lower injection pressures. For the vertebroplasty procedure, if cortical bone disruption is present, and the risk of cement leakage outside of the vertebral body, in the epidural space, or in the venous system, is increased, then coblation may be utilized. Coblation creates a cavity in the vertebral body with an FDA-approved low temperature radiofrequency device that ablates tumoral tissue through plasma ionization. Masala and colleagues treated patients with vertebral involvement by multiple myeloma with vertebroplasty alone. In this study of 64 patients with refractory pain to medical management, the average pre-procedure pain level on an analogue scale was 8.04 +/-1.4. At 1 and 6 months post-procedure the pain was reduced to 1.82 +/-1.84 and 1.92 +/-1.68.[6]

Therefore, in the setting of metastatic disease to the vertebrae, vertebroplasty can offer a means to provide earlier pain relief and structural stability compared to radiotherapy. Radiation adjuvantly may enhance pain control and eradicate cancer in the localized region. In a study of 57 patients with 78 sites of treated metastatic disease, the mean visual analogue scale (VAS) that measured pain was significantly decreased ($p<0.015$) one day after vertebroplasty and remained significant for 6 months following ($p<0.001$).[4] Assessment of vertebroplasty combined with radiotherapy in the setting of malignant tumor or hemangioma was performed in a study from South Korea.[5] Twenty-eight patients underwent percutaneous injection of polymethylmethacrylate into the collapsed vertebral bodies, with either a local anesthetic or general anesthesia for pain relief and spinal stabilization. Pain levels were assessed by using a VAS. The indications for vertebroplasty were an unstable or painful osteolytic metastatic tumor without associated neurological deficits. Inclusion criteria were vertebral collapse with or without pain or painful vertebra in the absence of collapse. If a radiculopathy was

present and not caused by encroachment of the tumor but by vertebral instability, then patients were still treated with vertebroplasty. Radiation therapy commenced immediately after the completion of the vertebroplasty procedure with the most common dosing schedule of 30Gy in fraction sizes of 3Gy. On day #3, VAS assessments showed that complete pain relief was achieved in 48% of patients and moderate relief in 41%. No major complications occurred in this study.*

In the setting of kyphoplasty at a median of 12 days previously, spinal radiosurgery was undertaken at the University of Pittsburgh. In this study, 26 patients, with metastatic vertebral fractures, having a total of 7 lesions previously undergone external-beam radiation therapy with spinal cord tolerance doses, were treated. Kyphoplasty was performed in all cases, at which time, gold fiducials were placed for future image guidance at the time of spinal radiosurgery. Sixteen Gy to 20Gy was delivered to the tumor with an improvement in back pain of 92% and no detectable neurological signs attributable to treatment during a follow-up period of 7-20months.[3]

A 2008 review article from Johns Hopkins confirmed that the VAS pain scores, narcotic usage and quality of life scales have all been shown to improve for over one year with vertebroplasty or kyphoplasty. Also, the procedures of vertebroplasty and kyphoplasty may be performed before, after or concurrently with most radiation protocols.[7]

** Pulmonary embolisms related to vertebroplasty-kyphoplasty usually refer to bone cement (PMMA) embolisms. Pulmonary PMMA embolism is detected in 5-10% of patients after vertebroplasty when a post-procedure chest plain film is obtained, and as high as in 25% of patients when a chest CT is obtained. In nearly all cases (in most large series those are ALL asymptomatic) these embolisms are asymptomatic, and have no clinical consequences at radiological and clinical follow-up, up to 24 months. Therapy is not warranted in patients with asymptomatic PMMA pulmonary embolism, so that several recent articles state no need for screening imaging studies after the procedure in asymptomatic patients*

1.3 Improvement in Quality of Life Measurement Tools

In assessing pain, quality of life, and overall response to treatment, various measurement tools have been employed by the previously quoted studies. The European Organisation of Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire assesses the pain level of the patient and the impact the pain has on daily life.

1.4 Potential Benefits of the Proposed Research to the Subjects and Others

The benefits being assessed are the possibilities of increased and earlier pain control, decreased fracture rate, and improved quality of life in comparison to historical measures. The risks are reasonable in regards to accomplishing these means given that currently both radiotherapy and vertebroplasty are in wide use as standard treatment options for these patients.

1.5 Importance of the Knowledge to be Gained

The knowledge gained from this study will help guide palliative therapy to optimize comfort and quality of life in the end-stages of life.

2.0 OBJECTIVES

2.1 Primary Objectives

Compare pain control assessed over time in patients treated with vertebral augmentation and radiation against a historical control group of metastatic patients treated solely with radiotherapy for pain and tumor control. Some of the subjects will undergo the vertebral augmentation first, others the Radiation first. Historical control rates will be taken from RTOG 9714 for pain control.

2.2 Secondary Objectives

2.2.1 Compare activity level prior to and following treatment. Historical control rates will be used for comparison.

2.2.2 Compare quality of life prior to and following treatment. Historical control rates will be used for comparison.

2.2.3 Fracture rates will also be compared against historical controls treated solely with radiotherapy. Historical control rates will be taken from RTOG 7402 for rates of fracture.

3.0 PATIENT SELECTION

To be eligible for the study, patients must fulfill all of the following criteria:

3.1 Conditions for Patient Eligibility

3.1.1 The diagnosis of metastatic disease will be fulfilled by one of two criteria: Previous pathological diagnosis of cancer with suspicion of metastatic disease on imaging, and clinical diagnosis of metastatic disease**.** If there is not pathological diagnosis, a specimen will be sent to pathology at the time of the surgery to confirm malignancy.

3.1.2 Appropriate diagnosis for protocol entry, based upon the following minimal diagnostic work-up:

- **3.1.2.1** History/physical examination within 8 weeks prior to registration and:.
- **3.1.2.2** Suspicion of metastatic cancer to the vertebrae or multiple myeloma with a focus in a vertebral body(ies) and;
- **3.1.2.3** The lesion must be identifiable with radiologic evidence (X-ray, bone scan, CT scan, MRI)**.**

3.1.3 Negative pregnancy test (urine dipstick or serum) for women of childbearing potential within 2 weeks prior to registration.

3.1.4 The patient must be an adult (18 years of age or older).

3.1.5 Life expectancy ≥3months AND KPS score ≥40 (see Appendix VIII – Legend).

3.1.6 **Pain scale score ≥ 5**

3.1.7 Indication for intervention:

3.1.6.1 Pain with a focus at the involved vertebral body that is not adequately controlled by medical management;

3.1.6.2 Osteolysis of a vertebral body(ies) with or without fracture at a site of metastatic infiltration/multiple myeloma, that poses risk of impending vertebral collapse. This is detected by the following cross-sectional imaging (MRI or CT) conditions[8]:

- In the **thoracic spine**:
  - A ≥ 50% involvement of the vertebral body with no destruction of other structures or;
  - A ≥ 25% involvement of the vertebral body associated with costovertebral joint destruction or posterior elements involvement.
- In the **lumbar spine**:
  - A ≥ 35% involvement of the vertebral body with no destruction of other structures or;
  - A ≥ 20% involvement of the vertebral body associated with involvement of posterior elements.

3.1.8 Women of childbearing potential and male participants must agree to practice adequate means of birth control throughout their participation in the study and for 6 months after their last treatment.

3.1.9 The patient must sign specific informed consent prior to study entry.

3.1.10 The patient is fully able to understand the English language so as to read and answer the study questionnaires.

3.1.11 Absence of any serious cognitive or psychiatric problems potentially hampering compliance with the study and follow-up schedule.

3.2 Conditions for Patient Ineligibility

3.2.1 Previous treatment defined as follows:

- Previous participation in this study.
- Previous radiotherapy to the site of vertebroplasty prior to study enrollment.
- Samarium therapy at any previous time.

3.2.2 Uncorrected coagulopathy:

- Plavix usage at the time of vertebroplasty or history of taking Plavix less than 7 days prior to procedure (In selected cases, radiation treatment can be initiated, the antiplatelet agent stopped, and vertebroplasty performed after 7days.)

3.2.3 Infection:

- Local infection at the puncture site
- Systemic infection, osteomyelitis, discitis

3.2.4 Anatomical considerations:

- If the patient has ≥ 4 sites. Only the 3 most painful sites of disease will be treated. Or, in the absence of pain, the 3 levels at greatest risk of impending collapse, based on extent of involvement, presence of posterior element involvement, or biomechanical risk based on location (mid-thoracic area, thoraco-lumbar junction, lumbosacral junction).
- Spinal cord compression with or without peridural spread
- Neurologic compromise due to spinal cord compression

3.2.5 Asymptomatic vertebral fracture and low risk for biomechanical instability and collapse.

3.2.6 Known allergy to any of the components used during vertebroplasty (PMMA bone cement)

3.2.7 Pain not localized to the region of metastatic disease. This may include:

- Diffuse non-focal back pain
- Radiculopathy

3.2.8 Inappropriate risk to the patient such as cardiorespiratory compromise such that safe conscious sedation or prone decubitus cannot be obtained.

3.2.9 Unable to obtain diagnostic imaging.

4.0 PATIENT CONSENTING/ SCREENING/ELIGIBILITY/REGISTRATION

4.1 Patient Consenting and Registration Process

Patients may be seen on an inpatient or outpatient basis. Patients will be approached by their treating physician regarding the study. If they are interested, someone from the Radiation Oncology Research Staff will go see the patient and give them a study specific consent form. If the patient is able to take the form home and discuss and/or discuss it with family members, they will be encouraged to do so. All Patients will be consented prior to entering this study. The consenting will be performed in a hospital room or clinic room with the door closed to maintain patient confidentiality. A member of the research team will read and review the consent with the patient (and family if available) and will answer questions. If needed, the treating physician will be brought in to answer any questions that the research staff member is unable to answer. The consent form will be signed (and HIPAA form) and a copy will be given to the patient. The patient will be assigned a sequential screening number beginning with HO-V-0001. This number will remain consistent with the subject even if the subject is determined ineligible, or does not receive study treatment or complete study follow-up.). The patient's chart will be reviewed and the following tests will be performed or reviewed to confirm eligibility. The patient will not need to repeat any of the tests if they have been performed in the time frame required by the study.

4.2 Within 8 weeks of prior to study treatment:
4.2.1 General History and Physical Examination
4.2.2 Karnofsky Performance Status
4.2.3 Bone scan, MRI, or CT of area to be treated
4.2.4 Status of pain from disease site to be treated (this is to ensure that eligibility criteria #8 is met.)
4.2.5 Platelet Count Blood Test
4.2.6 Adverse Event Check

4.3 Within 4 weeks of study treatment:
4.3.1 Fluoroscopy Imaging or plain film imaging at the time of vertebroplasty or if radiation is being done first, plain film will be performed prior to the radiation treatment. If vertebroplasty is done first, there will be no need for a plain film xray.

4.3.2 Adverse Event Check

4.4 Within 2 weeks prior to study treatment, patient will undergo:
4.4.1 Pregnancy test (urine dipstick or serum)
4.4.2 Adverse Event Check

Subjects may have the vertebral augmentation or the radiation first; whichever procedure is performed first, will be considered the beginning of study treatment.

5.0 PRETREATMENT EVALUATIONS/MANAGEMENT

After the patient's eligibility is determined, the following assessments will be performed:
5.1 Initial Assessment of Activity, Pain, and Quality of Life **(**All assessments will be done within 8 weeks prior to study treatment)
5.2.1 Worst Pain Score – BPI (Appendix I)
5.2.2 Roland-Morris Disability Questionnaire (Appendix II)
5.2.3 Pain Measurement Index and Narcotic Score (Appendix IV)
5.2.4 EORTC QLQ-C30 (Appendix III)
5.2.5 Baseline Data Collection Form (Appendix V)
5.2.6 Record of Current Pain Medications (Appendix VIII)

6.0 VERTEBRAL AUGMENTATION

All patients on the study must complete the vertebroplasty or kyphoplasty procedure within 0 - 4 weeks of registering for the protocol or within 0-4 weeks of completing radiation therapy (if radiotherapy is given first).
6.1 Treatment
6.1.1 1 – 3 sites of disease may be treated using conscious sedation (or general anesthesia) and intravenous antibiotic prophylaxis.
6.1.2 Fluoroscopy will be utilized to guide the procedure. In selected cases, the aid of CT may be added.
6.1.3 If there is only clinical and imaging documented disease, a biopsy will be obtained to confirm malignancy.
6.1.4 A cavity within the vertebra will be created with coblation technology when needed (largeosteolytic lesions, posterior wall erosion).
6.1.5 Adverse Events associated with this procedure are:
Potential toxicities include: bleeding at the site of puncture, in the paravertebral muscles, in the epidural space, or in the perivertebral soft tissues; pneumothorax; venous cement embolism to the epidural space, or to the systemic venous system; risk of nerve root or spinal cord compression; risk of pulmonary embolism; future vertebral fracture of the treated level or at adjacent levels; pain or weakness; paralysis; local or systemic infection. Some patients may suffer from a longer than average recovery period that may decrease their quality of life.
6.1.6 Post-procedure the following will occur (these are considered standard of care):

- Dressing at the puncture site
- Bed rest 2-3hrs prior to d/c (outpatients or 23hr hospitalization – if indicated)
- Monitor vitals & neurologic examination
- Gradual increase in activity over 3 days
- Physical therapy
- Medical treatment/Resume pain control as indicated

7.0 RADIATION THERAPY

All patients on study must start radiotherapy within 0 – 4 weeks of completion of the vertebral augmentation procedure if the vertebral augmentation procedure is done first.. If radiotherapy is completed prior to the vertebral augmentation procedure, it must be completed within 0-4 weeks of registration for the study.

7.1 Treatment

7.1.1 Palliative radiation to the focal region(s) of metastatic disease.

7.1.2 Radiation fractionation will be dependent on the patient health status and transportation status.
Options include:

- 30Gy in 10 fractions
- 20Gy in 5 fractions
- 8Gy in 1 fraction
- Multiple myeloma: local control dose (30Gy in 10 fractions)

7.1.3 Treatment portals will be left to the discretion of the radiation oncologist. All vertebral bodies treated with vertebroplasty/kyphoplasty will be encompassed in the treatment field(s).

7.1.4 Adverse Events of the Radiation Therapy include:
Potential toxicities include: fatigue; sore throat/difficulty swallowing; radiation pneumonitis; nausea/vomiting, alopecia; and/or skin darkening in the treatment field. Extremely rare but possible life-threatening side-effects include injury to the spinal cord that could cause pain or paralysis; and/or development of a secondary cancer due to radiation exposure.

8.0 MEASUREMENT OF RESPONSE/PATIENT FOLLOW-UP

The time of follow-up for all patients will be initiated immediately after completion of the initial procedure (vertebroplasty/kyphoplasty or radiotherapy). The patient grouping on Line 4 of the Baseline Data Collection Form will also correlate with the initial treatment.

8.1 1 Week Follow-Up Assessment

Assessment of the patient's pain, activities and quality of life will be gathered from the patient in returning for follow-up or by contacting the patient by phone approximately 1 week following the completion of their first procedure, whether it be the vertebral augmentation or the radiotherapy (5 – 10 days following). Mandatory assessments include:

8.1.1 Worst Pain Score – Brief Pain Inventory (BPI) (Appendix I)

8.1.2 Roland-Morris Disability Questionnaire (Appendix II)

8.1.3 Pain Measurement Index and Narcotic Score (Appendix IV)

8.1.4 Adverse Event Evaluation

8.2 1 Month Follow-Up Assessment

Assessment of the patient's pain, activities and quality of life will be gathered from the patient in returning for the 1 month follow-up appointment approximately 1 month following completion of the initial procedure whether it be the vertebral augmentation or the radiation therapy (3 – 5 weeks following). Mandatory assessments include:

8.2.1 Worst Pain Score – BPI (Appendix I)

8.2.2 Roland-Morris Disability Questionnaire (Appendix II)

8.2.3 EORTC QLQ-C30 (Appendix III)

8.2.4 Follow-Up Report (Appendix VI)

8.2.5 Pain Measurement Index and Narcotic Score (Appendix IV)

8.2.6 Record of Current Pain Medications (Appendix VIII)

8.2.7 Plain films of the vertebrae will be obtained if the patient's health status does not prevent him/her from travelling to the hospital.

8.2.8 Adverse Event Evaluation

8.3 3 Month Follow-Up Assessment

Assessment of the patient's pain, activities and quality of life will be gathered from the patient in returning for the 3 month follow-up appointment approximately 3 months following completion of the initial procedure whether it be the vertebral augmentation or the radiation therapy (10 – 14 weeks following). Mandatory assessments include:

8.3.1 Worst Pain Score – BPI (Appendix I)

8.3.2 Roland-Morris Disability Questionnaire (Appendix II) **8.3.3** Pain Measurement Index and Narcotic Score (Appendix IV)

8.3.4 Plain films of the vertebrae will be obtained if the patient's health status does not prevent him/her from travelling to the hospital.

8.3.5 Follow-up Report (Appendix VI)

8.3.6 Adverse Event Evaluation

8.3.7 **EORTC QLQ-30 (Appendix III)**

8.3.8 **Record of Current Pain Medications (Apendix VIII)**

9.0 QUALITY ASSURANCE

The Radiation Oncology Department holds a Dosimetry Meeting with physicians, physicists, and dosimetrists to discuss all patients undergoing radiation treatment. Radiation Oncology Co-chair will perform a Quality Assurance Review of all patients who receive treatment under the protocol. The goal of the review is to evaluate protocol compliance to determine that the radiation is given in accordance to this protocol.. All patients treated in the Radiation Oncology Clinic are presented at a peer review chart round meeting once per week.

Dr. Howell/Dr. Baaj will perform a Quality Assurance Review after complete data for the first 5 cases enrolled has been received. Dr. Howell/Dr. Baaj will perform the next reviews for subsequent blocks of 5 cases after the complete data for these cases becomes available at the University. The final cases will be reviewed within 3 months after this study has reached the target accrual.

10.0 PROTOCOL DATA AND SAFETY MONITORING PLAN (MEDIUM RISK)

Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are not designated as high risk per NCI, do not meet the above criteria of medium plus IND risk, and do not require an the IND (i.e. IND exempt).

10.1 Data and Safety Monitoring Plan:

10.1.1 Identification of the DSMB obligated for oversight responsibilities:
The Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial.

10.1.2 Identification of the entity obligated for routine monitoring duties:
Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

10.1.3 Monitoring progress and data review process:
Routine monitoring of subject data will be conducted at least every six months.
The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;
- Subject eligibility - 50% of cases, up to two subjects;
- Data review - 50% of cases, up to two subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. A query/finding form or an electronic record will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the CRF and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form, or will be notified of the electronic record for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit. Electronic records will be available in the institution database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form, adverse event forms and serious adverse event forms [other forms, depending on study] should be completed via the institution database or other acceptable data formats. Trials using paper CRFs will have the data entered with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All subject forms and study files will be stored in a secure area limited to authorized staff

Note: Routine monitoring of regulatory documents and test article will be conducted at least annually.

10.1.4 Process to implement study closure when significant risks or benefits are identified: If there is a grade 5 toxicity of any kind related to the study procedures reported in two of the patients, the study will be discontinued.

10.2 Adverse Events

10.2.1 An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.2.2 Any and all adverse events will be recorded on the UMC adverse events record form and reviewed by the Principal Investigator.

10.2.3 All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (A copy of the CTCAE version 4.0 can be downloaded from the National Cancer Institute, Adverse Event Reporting Guidelines http://ctep.cancer.gov) and will address:
10.2.3.1 Grade

10.2.3.2 Relationship to study drug(not related, unlikely, possible, probable, definitely)
10.2.3.3 Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
10.2.3.4 Date of onset, date of resolution
10.2.3.5 Frequency of event (single, intermittent, continuous)
10.2.3.6 Event outcome (resolved, ongoing, death)
10.2.3.7 Action taken (none, held, dose reduced, discontinued, medication given)

10.2.4 If an adverse event should arise during radiotherapy that is felt to increase the likelihood of patient mortality or morbidity greater than the benefit provided, than radiotherapy may be stopped. If the patient should experience a consequence of vertebral augmentation then he/she may still proceed with radiotherapy for pain relief. All other side-effects may be treated medically as clinically indicated.

10.3 Serious Adverse Events

10.3.1 A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

1) Results in death;
2) Is life-threatening;
3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
4) Results in disability persistent or significant disability/incapacity, or:
5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

10.3.2 All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and DSMB Coordinator and the study PI. For both serious and non-serious adverse events, the investigator must determine both the intensity of the event and the relationship of the event to the study. All serious adverse events will be reported to the University of Arizona Human Subjects Protection Program according to their policies and procedures.

10.3.3 All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB, every six months. The DSMB coordinator will review the SAE reporting process to confirm reporting requirements are met.

10.4 Plan for Assuring Data Accuracy and Protocol Compliance:

10.4.1 Routine study activity and safety information will be reported to the DSMB every six months, or more frequently if requested. These reports will include:
10.4.1.1 Study activity, cumulative and for the period under review;
10.4.1.2 Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
10.4.1.3 Predetermined protocol early stopping rules for efficacy/futility;
10.4.1.4 Status of study in relationship to stopping rules;
10.4.1.5 Current dose level of study agent;
10.4.1.6 Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
10.4.1.7 Comments;
10.4.1.8 Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies

10.4.2 Data, safety and study progress will be reported to:
10.4.2.1 Human Subjects Protection Program (IRB) at least annually;
10.4.2.2 Sponsor (if applicable) at least every six months.

10.4.3 Identification of the sponsor or funding agency, as applicable:
The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study. A copy of this correspondence will also be forwarded to the DSMB and the SRC.

11.0 OTHER THERAPY

11.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented. This may include but is not limited to:

- Narcotics for pain control
- Bisphosphonates
- Hormone Therapy
- Chemotherapy

12.0 TISSUE/SPECIMEN SUBMISSION

A tissue biopsy will be collected at the time of vertebroplasty for confirmation of malignancy for those patients without a previous diagnosis of metastatic cancer or multiple myeloma.

13.0 PATIENT ASSESSMENTS

A series of patient questionnaires will be mandatory at the patient evaluation and intervals after completing treatment to assess for pain control, quality of life and films performed to determine fracture rates post-treatment.

13.1 Pain Assessment Tools

13.1.1 Worst Pain Score – BPI

The Worst Pain Score – BPI will provide pain measures. Pain rating scale from 0 – 10 with 0 representing no pain and 10 representing the worst pain possible. Prior to treatment patients will be asked to rank their current pain intensity and also pain within the last 24hours at its worst, while not being controlled with narcotics. Patients considered to have painful metastasis, at least 5 on a scale of 10, will be evaluated for control of pain. Patients will be judged as having a complete response if the pain is scored as 0 after the procedure(s). A partial response is determined as when the pain rating is $\geq$2 points lower than before the procedure(s). A stable response is 1 point change in either direction on the pain scale. Progressive pain will be considered an increase of $\geq$2 points on the pain scale. Those patients not initially having pain (<5 on the pain scale) will be monitored for an increase in pain score ($\geq$5 AND an increase of $\geq$2 points) versus stable response (1 point change in either direction OR overall score 0-4). See Appendix I.

13.1.2 Pain Measure Index

Enable measurement of pain by assessing narcotic usage. See appendix IV for further details.

13.2 Assessment of Patient Activities

13.2.1 Roland-Morris Disability Questionnaire

Brief survey detailing the amount of time the patient can tolerate activities of daily living. See appendix II for further details.

13.3 Assessment of Quality of Life

13.3.1 EORTC QLQ-C30 (version 3)

The EORTC QLQ-C30 is the most frequently used measure in cancer clinical trial research and is well established as a quality of life instrument for cancer patients in general. See appendix III for further details.

13.3.2 Baseline Data Collection Form

See appendix V for further details.

13.3.3 Follow-Up Report

See appendix VI for further details.

13.4 Assessment of Fracture Rate

Plain films will be acquired at 1 month and 3 months status post treatment. The height of the vertebral body will be compared with the height as determined on fluoroscopy at the time of VA. A loss of height of >10% will be considered an increase in the compression fracture of the vertebrae. Fractures in adjacent vertebra will also be noted. The fracture rate will be documented as fracture (yes/no) per vertebral body.

13.5 Criteria for Removal from Protocol Treatment

13.5.1 Unacceptable adverse event(s) to the patient (at the discretion of the treating physician) – Reasons for removal must be clearly documented in the patient's records.

13.5.2 The investigators or treating physician may withdraw the patient from protocol treatment if it is felt to be in the patient's best interest. The reasons for removal must be clearly documented in the patient's records.

13.5.3 Patients discontinuing the treatment portion of the protocol should continue to be followed for study endpoints.

14.0 DATA COLLECTION

14.1 In-House Data Collection and Analysis

The data collected for this study will be kept in the patient's research charts and will be identified by both patient name and medical record number. A secure computer database will be constructed to house the data for statistical analyses and interpretation.

14.1.1 Summary of Data Available for Study Analysis

- Patient consultations
- Radiographic images relevant to diagnosis and treatment (MRI, CT, Bone Scan, Plain Films, Fluoroscopy)
- Procedure Notes
- On Treatment Visits
- Treatment Summary Notes
- In-Patient Notes as related to possible complications
- Follow-Up Notes
- Follow-Up radiographic images of the area of treatment
- Worst Pain Score as rated on the Brief Pain Inventory Scale (BPI)
- Roland-Morris Disability Questionnaire
- EORTC QLQ-C30Baseline Data Collection Form
- Pain Measurement Index and Narcotic Score
- Follow-Up Report (supplement to the EORTC questionnaires)
- Record of Current Pain Medications

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Endpoints

15.1.1 Primary Endpoint:

Total change in pain status will be calculated as the difference between the pain score at 3 months and the pain score at baseline. A decrease from baseline to 3 months of 2 or more points or no pain at 3 months is considered a positive **outcome** and the rate of pain control is defined as the proportion of patients with a positive outcome. From the RTOG 9714 experience, this is the complete plus partial response rate at a 3 month follow-up time period.

15.1.2 Secondary Endpoints:

Change from baseline to other points in time for pain will be calculated. Activity level prior to and following treatment will be assessed using the difference between the activity level at 3 months and the activity level at baseline. Quality of life prior to and following treatment will be calculated by subtracting baseline quality of life measure(s) from the measures taken at follow-up time points. Fractures per patient will be assessed at 1 and 3 months and recorded as a binary variable (yes/no). Fractures will be counted as the involvement per each vertebral body. In analysis this will be compared to RTOG 7402 fracture rates. Any increase in compression of a vertebra by $\geq$10% by imaging will be considered positive for development of a fracture. Toxicity will be graded according to CTCAE 3.0 for each patient.

15.2 Analytic Plan

15.2.1 Analysis of Primary Endpoint: The proportion of patients that experience a change in pain from baseline to 3 months of at least 2 or more points (or improve to no pain) will be estimated with its 95% confidence interval. The historical control rate of pain control, defined in the same way, in RTOG 9714 was 66%. We will use an exact binomial test with a one-sided alpha of 0.05 to test the null hypothesis that the pain control rate in our study is 65%.

15.2.2 Analysis of Secondary Endpoints: Graphical displays will be used to show scores over time. Changes from baseline to follow-up will be calculated and tested for significance using paired t-tests of non-parametric tests. The rate of fractures will be estimated as a proportion with its 95% confidence interval. It will be compared to the fracture rate from RTOG 7402 (6% spinal sites) using an exact binomial test. The study is not powered to detect a difference in fracture rates and only very large differences will be detectable.

15.3 Sample Size

Given the average number of patients treated in 1 month at a comparable cancer center, 25 patients with painful metastasis may be accrued within our department in a time frame of 1-2 years. This will allow for approximately 5 patients being deemed ineligible or not completing study treatment or follow-up. With 20 patients and a null pain control rate at 3 months of 65%, we can detect a pain control rate of 89% with 83% power using a one-sided alpha of 0.05.

Projected Distribution of Gender

Gender Category	Percentage	Absolute
Females	55%	11
Males	45%	9
Total	100%	20 patients

REFERENCES

1. Daphne Tong, Laurence Gillick, et al. The Palliation of Symptomatic Osseous Metastases: Final Results of the Study by the Radiation Therapy Oncology Group. Cancer 50:893-899, 1982.

2. William F. Hartsell, Charles B. Scott, et al. Randomized Trial of Short- Versus Long-Course Radiotherapy for Palliation of Painful Bone Metastases. Journal of the National Cancer Institute 97(11):798-904, 2005.

3. Peter C. Gerszten, Anand Germanwala, et al. Combination Kyphoplasty and Spinal Radiosurgery: a New Treatment Paradigm for Pathological Fractures. Neurosurg Focus 18(3):E8, 2005.

4. Y.-Y. Tseng, S.-T. Tang et al. Minimally Invasive Vertebroplasty in the Treatment of Pain Induced by Spinal Metastatic Tumor. Minim Invas Neurosurg 51:280-284, 2008.

5. Jee-Soo Jang, MD, and Sang-Ho Lee, MD. Efficacy of Percutaneous Vertebroplasty Combined with Radiotherapy in Osteolytic Metastatic Spinal Tumors. J. Neurosurg Spine 2:243-248, 2005.

6. Salvatore Masala, Giovanni Anselmetti, et al. Percutaneous Vertebroplasty in Multiple Myeloma Vertebral Involvement. J Spinal Disord Tech 21(5), July 2008.

7. John Chi and Ziya Gokaslan. Vertebroplasty and kyphoplasty for spinal metastases. Current Opinion in Supportive & Palliative Care. 2(1):9-13, March 2008.

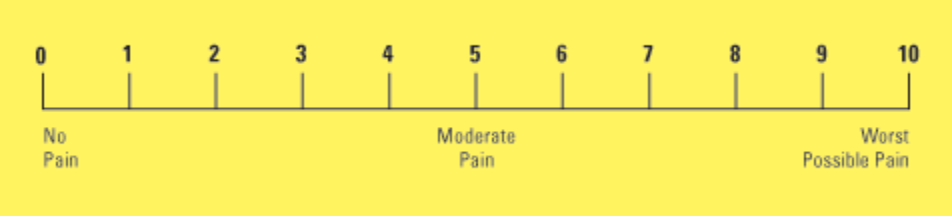
8. B.A. Georgy. Metastatic Spinal Lesions: State-of-the-Art Treatment Options and Future Trends. American Journal of Neuroradiology. 29:1605-11, October 2008.

APPENDIX I

Worst Pain Assessment on the Brief Pain Inventory Scale[1]

The Worst Pain Assessment on the Brief Inventory Scale is an assessment tool of current pain intensity and pain intensity within the last 24 hours when not on pain control medications.

Please scale the intensity of your pain within the last 24hours on the scale below. 0 being no pain and 10 is the worst pain possible.



1 *Serlin RC, Mendoza TR, Nakamura Y, Edward KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995;61 277-84.*

APPENDIX II

Roland-Morris Disability Questionnaire[1]

As you read the list, think of yourself *today*. When you read a sentence that describes you today, put a tick against it. If the sentence does not describe you, then leave the space blank and go on to the next one.

Remember, only tick the sentence if you are sure it describes you today.

1. I stay at home most of the time because of my back.
2. I change position frequently to try and get my back comfortable.
3. I walk more slowly than usual because of my back.
4. Because of my back I am not doing any of the jobs that I usually do around the house.
5. Because of my back, I use a handrail to get upstairs.
6. Because of my back, I lie down to rest more often.
7. Because of my back, I have to hold on to something to get out of an easy chair.
8. Because of my back, I try to get other people to do things for me.
9. I get dressed more slowly then usual because of my back.
10. I only stand for short periods of time because of my back.
11. Because of my back, I try not to bend or kneel down.
12. I find it difficult to get out of a chair because of my back.
13. My back is painful almost all the time.
14. I find it difficult to turn over in bed because of my back.
15. My appetite is not very good because of my back pain.
16. I have trouble putting on my socks (or stockings) because of the pain in my back.
17. I only walk short distances because of my back.
18. I sleep less well because of my back.
19. Because of my back pain, I get dressed with help from someone else.
20. I sit down for most of the day because of my back.
21. I avoid heavy jobs around the house because of my back.
22. Because of my back pain, I am more irritable and bad tempered with people than usual.
23. Because of my back, I go upstairs more slowly than usual.
24. I stay in bed most of the time because of my back.

Scoring:
The score of the RDQ is the total number of items checked – i.e. from a minimum of 0 to a maximum of 24.

1. Roland MO, Morris RW. A study of the natural history of back pain. Part 1: Development of a reliable and sensitive measure of disability in low back pain. Spine 1983; 8: 141-144

APPENDIX III

Study ID: _____
Date: _____
Country: _____

Please Circle:
Group: A B C D E F G

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities,	1	2	3	4
	like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing	1	2	3	4
	yourself or using the toilet?				

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other	1	2	3	4
	leisure time activities?				
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1 2 3 4 5 6 7

Very poor Excellent

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

1 2 3 4 5 6 7

Very poor Excellent

APPENDIX IV

PAIN MEASURES INDEX AND NARCOTIC SCORE[1]

I. Severity of pain at treatment site
- 0: None
- 1: Mild
- 2: Moderate
- 3: Severe

II. Frequency of pain at treatment site
- 0: No pain
- 1: Occasional (less than daily)
- 2: Intermittent (at least once a day)
- 3: Constant (most of the time)

III. Type of pain medication administered
- 0: None
- 1: Analgesic (aspirin, bufferin, anacin, darvon)
- 2: Mild narcotic (one-half gram codeine, percodan, etc.)
- 3: Strong narcotic (one gram or more of codeine, morphine, demerol, etc)

IV. Frequency of pain medication administration
- 0: None
- 1: Less than daily
- 2: Once per daily
- 3: More frequently than once per day

V. Pain Score = (pain severity) x (pain frequency)

VI. Narcotic score = (medication type) x (medication frequency)

[1]Daphne Tong, Laurence Gillick, et al. The palliation of symptomatic osseous metastases: final results of the study by the radiation therapy oncology group. Cancer 50:893-899, 1982.

APPENDIX V

BASELINE DATA COLLECTION FORM

1. Patient Name:

2. Patient Date of Birth:

3. Date of Visit:

4. Patient Status *(please circle)*:

Inpatient Outpatient

5. Karnofsky Performance Status (please refer to table below):

6. Date of Interview:

7. Patient allergies: _____

8. Current Age:

9. Gender *(please circle):*

Male Female

10. Marital Status *(please circle)*:

Single Partner (unmarried) Married Widowed Other
Specify: _____

11. Cohabitants *(please circle)*:

Alone Spouse Spouse & child(ren) Child(ren) Other
Specify: _____

12. Primary Cancer Site *(please circle)*:

Breast Prostate Lung Multiple Myeloma Colorectal

Renal Cell/Kidney Stomach Oesophagus Pancreas Liver

Ovarian Other
Specify: _____

13. Year of Diagnosis of Primary Cancer:

14. Year of Diagnosis of Bone Metastases:

15. Number of Bone Metastases *(please circle)*:

1 2 3

16. Level of vertebral bodies involved:

1 2 3

179. Other Sites of Metastasis (if known) *(please circle)*:

Lymph Lung Brain Liver Other
Specify: _____

18. Skeletal Related Event? *(please circle):* Yes No

If "Yes", please answer items 18 a) to e)

a) Radiotherapy for Bone Metastases *(please circle)*: Yes No Date of Last Treatment:

b) Pathological Fracture *(please circle)*: Yes No Date of Diagnosis:

c) Spinal Cord/Cauda Equina Compression *(please circle)*: Yes No Date of Diagnosis:

d) Orthopaedic Surgery *(please circle)*: Yes No Date of Surgery:

e) Hypercalcaemia *(please circle)*: Yes No Date of Diagnosis:

19. Previous Systemic Treatment? *(please circle):* Yes No

If "Yes", please answer items 19 a) to c)

a) Chemotherapy *(please circle)*: Yes No Date of Last Treatment:

b) Bisphosphonate *(please circle)*: Yes No Date of Last Treatment:

c) Hormone Therapy *(please circle)*: Yes No Date of Last Treatment:

NOTES

APPENDIX VI

FOLLOW-UP REPORT

1. Study I.D.:	Patient Initials:
2. Date of Interview:	
3. Patient Status *(please circle)*:	
Inpatient	Outpatient
4. Karnofsky Performance Status (please refer to table below):	
5. Skeletal Related Event **since completion of treatment or last follow-up?** *(please circle)*:	
Yes	No
If "Yes", please answer items 6 a) to e)	
a) Radiotherapy for Bone Metastases *(please circle)*: Yes No Date of Last Treatment:	
b) Pathological Fracture *(please circle)*: Yes No Date of Diagnosis:	
c) Spinal Cord/Cauda Equina Compression *(please circle)*: Yes No Date of Diagnosis:	
d) Orthopaedic Surgery *(please circle)*: Yes No Date of Surgery:	
e) Hypercalcaemia *(please circle)*: Yes No Date of Diagnosis:	
6. Change in Systemic Treatment **since completion of treatment or last follow-up?** *(please circle):*	
Yes	No
If "Yes", please answer items 7 a) to c)	
a) Chemotherapy *(please circle)*: Yes No Date of Last Treatment:	
b) Bisphosphonate *(please circle)*: Yes No Date of Last Treatment:	
c) Hormone Therapy *(please circle)*: Yes No Date of Last Treatment:	
7. Hospitalization **since completion of treatment of last follow-up?***(please circle):*	
Yes	No
If "Yes", please answer item 8 a)	
a) Hospitalization Related to Bone Metastases? *(please circle)*: Yes No Details:	
NOTES	

Appendix VII

Karnofsky Performance Status (KPS)
Description
100 - Normal, no complaints, no evidence of disease.
90 - Able to carry on normal activity; minor signs or symptoms of disease.
80 - Normal activity with effort; some signs or symptoms of disease.
70 - Cares for self, unable to carry on normal activity or do active work.
60 - Requires occasional assistance, but is able to care for most of his/her needs.
50 - Requires considerable assistance and frequent medical care.
40 - Disabled, requires special care and assistance.
30 - Severely disabled, hospitalization indicated. Death not imminent.
20 - Very sick, hospitalization indicated. Death not imminent.
10 - Moribund, fatal processes progressing rapidly.

Appendix VIII

RECORD OF CURRENT PAIN MEDICATIONS

Please write ALL the regular pain medications you have been taking during the past 24 hours.
(If using a fentanyl patch, or "Duragesic", please indicate strength of each patch.)

Please write ALL the breakthrough pain medications you have been taking during the past 24 hours.

Name of Medication	Route of Administration	Strength (mg)	Number of Pills/ Administrations per day

* Possible routes: oral / intravenous / subcutaneous / rectal / patch / sublingual (under tongue) / intramuscular

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:

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

Please rate your pain by circling the one number that best describes your pain at its **worst** during the past day.

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

APPENDIX IX
STUDY PARAMETER TABLE

	Pre-treatment (within 8 wks prior to treatment)	Pre-treatment (within 4 weeks of treatment)	Pre-treatment (within 2 weeks of treatment	At time of VA or Radiotherapy	1 week follow-up (5 – 9 days following initial procedure)	1 month follow-up (3 – 5 weeks following initial procedure)	3 month follow-up (10 – 14 weeks following initial procedure)
History/physical (including KPS)	x						
Imaging (X-ray, bone scan, CT scan or MRI)	x						
B-HCG (if applicable)			x				
Fluoroscopy				X[2]			
Plain film Imaging		X[2]					
Worst Pain Score - BPI	x				x	x	x
Roland-Morris Disability Questionnaire	x				x	x	x
EORTC QLQ-C30	x					x	
Baseline Data Collection Form	x						
Pain Measurement Index and Narcotic Score	x				x	x	x
Follow-Up Report						x	x
Record of Current Pain Medications	x				x	x	
Plain films						x	x
Biopsy				x[1]			
Adverse event evaluation		x	x	x	x	x	x

1 If no previous pathology confirmation, a biopsy will be collected at the time of the Vertebral Augmentation

2 [2] Fluoroscopy will be done at time of vertebral augmentation, If radiation is done firs, a plain film Xray will be done prior to radiation treatment