

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6661

A PHASE I/II STUDY OF PERCUTANEOUS RADIOFREQUENCY ABLATION OF BONE METASTASES USING CT GUIDANCE

***PARTIAL PROTOCOL-
CONTACT ACRIN PROTOCOL
DEVELOPMENT AND
REGULATORY COMPLIANCE
FOR A COMPLETE PROTOCOL***

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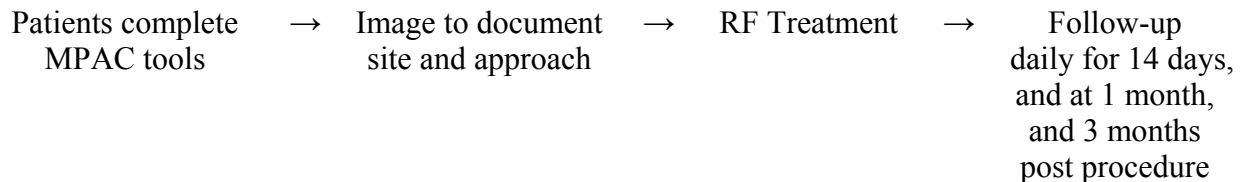
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SCHEMA

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Eligibility Criteria (See Section 4.0 for details)

- Histologically or cytologically documented malignant disease with a new bone lesion that has the clinical and/imaging features of metastatic disease. Patients with primary musculoskeletal malignancies, lymphoma and leukemia will not be RFA treatment candidates.
- Persistent intractable pain that resulted in a return visit to the oncologist. The measurable pain must be above a pain scale of **five** (scale of 0-10). (Pain during the last week described as “the worst” (as measured by VASPI) by the patient on a scale of 0 (no pain) to 10 (pain as bad as patient can imagine).
- The patient's pain must be from a solitary site of metastatic disease in the bone. Each site must be amenable to RFA utilizing a percutaneous CT-guided approach. (RF electrode can be safely placed under CT guidance without harm to normal structures.)
- The maximum size of the bone metastasis must be no greater 8 cm.
- Radiofrequency treatment can be performed within 5 days of baseline evaluations.
- The tumor mass must not come in contact with hollow viscera.
- Patients are not eligible if they have uncontrolled coagulopathy or bleeding diathesis. Platelets must be $\geq 70,000/\text{ul}$.
- Patients must be cognitively intact and all patients must sign informed written consent.
- Aspirin and nonsteroidal anti-inflammatory medications, antiplatelet medications, or warfarin must be discontinued prior to the procedure for a time period that is appropriate given the drug half life and the drugs known antiplatelet activity (e.g., aspirin for 7 days and ibuprofen 24 hours). Low molecular weight heparin preparations must be discontinued 24 hours prior to procedure.
- Patients must not have a pacemaker.

Required Sample size: 75 patients to be recruited in 12.5 months

1.0 ABSTRACT

Pain from osseous metastatic disease is by far the commonest cause of cancer pain. Conventional treatment of osseous metastatic disease has relied primarily on external beam radiation and chemotherapy. Current treatment does not effectively handle this complex group of patients and many patients die with inadequate analgesia. Radiofrequency ablation (*RFA*) is an image-guided minimally invasive treatment for solid tumors. Patients that have not responded to conventional treatment may benefit from palliation with RFA. We propose to study a group of patients that have persistent pain from a solitary focus of metastatic disease that may or may not have been previously treated. Patients will have their pain quantified with visual analog pain scales prior to and after treatment. Adverse events from the RFA will be recorded. The contrast-enhanced CT and/or MRI imaging appearances of the treated area will also be analyzed and correlated with the treatment effects.

2.0 BACKGROUND AND SIGNIFICANCE

Metastatic cancer is the most common neoplasm involving the skeletal system.¹ Of approximately 965,000 new cancer cases each year in the United States, approximately 30-70% will develop skeletal metastases. Given the high prevalence of carcinomas of the breast, lung and prostate, these cancers account for more than 80% of cases of metastatic bone disease. Bone metastases lead to significant morbidity due to pain, pathologic fracture, and neural compression.

Pain from bone metastases can be related to mechanical or chemical factors. Pressure effects on the periosteum or adjacent neural structures can cause local or radiating pain. Hemorrhage from local bone osteolysis by osteoclastic activity causes a local release of bradykinin, prostaglandins, histamine and substance P that can irritate the endosteal nerves as well as local nerves.²

Primary treatment has relied upon radiation therapy³ with or without systemic chemotherapy or hormonal therapy. Newer systemic treatments with radionuclides^{4,5} and bisphosphonates^{6,7} have also shown some success. Radiation therapy works by killing the local tumor and inflammatory cells that are responsible for causing the pain. Many prospective trials have been performed studying the ability of external beam radiation therapy to palliate pain or control progression of osseous metastatic disease.⁸⁻¹⁵ The Radiation Therapy Oncology Group study by Tong et al.⁸ measured the patient's response to radiation therapy with a pain scale and narcotic requirement scale of 1-4. Two hundred and sixty-six of the 1016 patients studied had a solitary metastasis. The study showed a complete response rate of 54% and a partial response rate of 90%. Ninety-six percent of the patients had at least minimal relief within the first 4 weeks and only 50% had complete relief in 4 weeks. There was a 30% relapse rate within the patients who survived at least 12 weeks. Patients in the study with lung cancer or with severe constant pain at the outset tended not to improve after radiation. Madsen reported a response rate of only 48% when measuring a patient's pain using a visual analog scale.⁹ Overall response rates vary according to the length of follow-up, type of radiation treatment and the measurement of patient response. As pointed out by a review of all published reports by Ratanatharathorn et al.¹⁶ the relapse after initial response is frequent, the pain relief in all studies is poor and the practices of radiation therapy need to be improved.

Surgical therapy is applied in certain instances where mechanical strengthening is necessary such as an impending fracture. These therapies are often unsuccessful in pain reduction and patients may require significant doses of narcotics. Therefore, a more effective modality of local treatment for bone metastases could substantially improve quality of life. The life expectancy of

patients with osseous metastatic disease is limited with an average median survival of between 3-6 months. Therefore, finding an effective local therapy that can be done at a single outpatient sitting would be beneficial.

Recently percutaneous procedures for providing local tumor ablative therapy such as ethanol injection,¹⁷ vertebroplasty¹⁸ and radiofrequency ablation (RFA)^{19,20} have shown some promise in the treatment of metastatic bone lesions. Spinal RFA for metastatic disease can be safely performed in the presence of an intact vertebral body cortex because cortical bone acts as an insulator and cerebrospinal fluid pulsations as well as the basivertebral venous plexus act as heat sinks to the RF energy.¹⁹ Percutaneous RFA is a technique that was originally pioneered decades ago for the treatment of trigeminal neuralgia.²¹ For the treatment of bone lesions the technique involves placing an electrode under CT guidance directly into the metastasis. The electrode is coupled to a radiofrequency generator and causes tissue necrosis by heating of adjacent tissues. The potential advantages of RFA versus other destructive methods are multifold: cell death is immediate, lesion size can be accurately controlled, lesion temperature can be monitored, electrode placement can be achieved with a percutaneous image-guided procedure, and radiofrequency lesions can be performed under local anesthesia and conscious sedation. Today RFA is commonly used in the musculoskeletal system for treatment of intractable back pain due to failed back syndrome²², and chronic back pain due to facet joint osteoarthritis.²³ CT-guided RFA has been shown to be a cost effective surgical alternative in the treatment of osteoid osteomas.²⁰ A recent preliminary study investigated RFA for patients with metastatic bone tumors that remain painful after radiation therapy or are solitary and can be treated without subjecting the bone marrow to immunosuppressive doses of external beam radiation therapy. Subjective pain relief has been reported.²⁴ We have just completed a pilot study in which we treated 18 metastatic bone tumors in 16 patients. By the visual analogue pain scale of 0 (*no pain*), to 10 (*worst*), the mean of average pain intensity was 6.5 prior to RFA and 4.62, at 1 week ($P = 0.039$) and 4.64, at 1 month ($P = 0.036$) after the procedure. Similarly the mean of the worst pain described by the patients was 8.5 before the procedure, and was 6.93 ($P = 0.005$) and 5.64 ($P = 0.003$) one week and one month, respectively. No incidences of bleeding or infection at the site of procedure were reported and the only side effects were swelling at the site (*1 pt.*) limited pain at the site (*1*) and flu like symptoms (*1*). Patients with larger tumors involving the pelvis and sacro-iliac joints did not show significant pain relief. However, patients with smaller tumors and tumors involving the chest wall had significant pain relief. We now propose to formally evaluate RFA in a phase I/II study for patients with bone metastases.

The outcomes of the study will be adverse event analysis and pain relief.

2.1 Pain Relief

Pain relief will be objectively measured before and after RFA using the Memorial Pain Assessment Cards (MPAC) developed at the Memorial Sloan Kettering Cancer Center.²⁵ Patients will serve as their own internal control and the pain relief will be studied over a three-month period of time. Due to the placebo effect and the regression-to-the mean phenomenon daily pain scales will be performed for 5 days prior to the procedure and 14 days after the procedure. This system has been shown to be a valid, reliable and sensitive measure of cancer pain. The MPAC was chosen over other pain assessment instruments because it is a simple efficient means of quantifying pain. This makes it more suitable for medically ill patients. Changes in the severity of pain before and after RFA will be statistically analyzed.

2.2 Narcotic Quantification

Patients will undergo stabilization of narcotic usage one week prior to RFA. The narcotics used as well as dosage and frequency will be recorded in a pain medication diary and recorded daily starting from one week pre-RFA to daily for 14 days post treatment as well as one month and three months.

2.3 Adverse Event and Toxicity Analysis

All toxicities related to the RFA procedure will be recorded using the Common Toxicity Criteria version 2.0 developed by the National Cancer Institute (*see Section 12.0 Adverse Event Reporting*). Any toxicity of a grade 3 or 4 will be considered an adverse event. Adverse events of less severity are reported on case report forms and submitted with routine data submission.

3.0 SPECIFIC AIMS

3.1 Primary Aim

3.1.1 To determine the side effects of RFA and its effect on pain in patients with osseous metastatic disease. If pain control can be safely and effectively achieved with RFA in this initial study, then a future goal is to perform a prospective randomized trial comparing RFA and external beam radiotherapy in patients with focal painful osseous metastatic disease.

3.2 Secondary Aims

3.2.1 To determine how RFA affects the mood in patients with painful osseous metastatic disease.

3.2.2 To determine the effects of narcotic usage after RFA.

3.2.3 To analyze the laboratory and imaging features of RFA and how they may relate to the treatment effects.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

4.1.1 Histologically or cytologically documented malignant disease with a bone lesion that has the clinical and/imaging features of metastatic disease.

4.1.2 Persistent intractable pain that results in a return visit to the oncologist. The measurable pain must be above a pain scale of **five** (*scale of 0-10*). (*Pain during the last week described as “the worst” by the patient on a scale of 0 (no pain) to 10 (pain as bad as patient can imagine)*).

4.1.3 The patient's pain must be from a solitary site of metastatic disease in the bone. Each site must be amenable to RFA utilizing a percutaneous CT-guided approach. (*RF electrode can be safely placed under CT guidance without harm to normal structures.*)

4.1.4 The maximum size of the bone metastasis (study site) must be no greater than 8 cm.

4.1.5 Radiofrequency treatment can be performed within 5 days of baseline evaluations.

4.1.6 All patients must understand and sign a study-specific informed consent.

4.2 Exclusion Criteria

- 4.2.1 Tumor mass in contact with hollow viscera.
- 4.2.2 Uncontrolled coagulopathy or bleeding diathesis that cannot be corrected with FFP and platelets prior to procedure. (*Platelets must be $\geq 70,000/\mu\text{l}$.*)
- 4.2.3 Aspirin and nonsteroidal anti-inflammatory medications, antiplatelet medications, or warfarin must be discontinued prior to the procedure for a time period that is appropriate given the drug half life and the drugs known antiplatelet activity (e.g. aspirin for 7 days and ibuprofen 24 hours). Low molecular weight heparin preparations must be discontinued 24 hours prior to procedure.
- 4.2.4 Tumor involves a weight-bearing long-bone of the lower extremity.
- 4.2.5 Site of tumor surgically stabilized with metallic hardware.
- 4.2.6 Previous (*within 30 days immediately prior to RFA or post RFA*) or scheduled concurrent systemic treatment of metastases with external beam radiation or radioisotopes. (*Chemotherapy will not be allowed within 14 days prior to and within 14 days post RFA procedure*).
- 4.2.7 Patients with primary musculoskeletal malignancies, lymphoma and leukemia will not be RFA treatment candidates.
- 4.2.8 Spinal metastases that do not have an intact cortex between the mass and the spinal canal and exiting nerve roots.
- 4.2.8 Patients with a pacemaker.

5.0 SITE SELECTION

5.1 Institution Requirements

5.2.1 IRB Approval and Informed Consent

All institutions must have study-specific IRB approval. RA's must follow the Office of Human Research Protections (**OHRP**) approved consent procedures, as well as those set by the Institutional Review Board (**IRB**) at the institution. A copy of IRB approval and the sample institutional study-specific consent form must be on file at ACRIN Headquarters (fax 215-717-0936) prior to registering your first patient. (Sample informed consent is in Appendix I.)

5.2.2 Applications

Site must have completed and sent in the ACRIN general and protocol specific applications for approval. (See Appendix II for protocol specific application.)

6.0 ONLINE REGISTRATION AND RANDOMIZATION SYSTEM

6.1 Using the Online Registration System

- 6.1.1 Once the Research Associate (RA) has completed the eligibility form and the patient has been found to be eligible, the patient may be consented. The RA will register the patient by logging onto the ACRIN web site (www.acrin.org) and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (*OHRP assurance, IRB approval*) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was

completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist and the date the study-specific informed consent form was signed.

6.1.2 Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen, which confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC and generates a data submission calendar listing all data forms, images and reports and the dates on which they are due.

6.2 Unsuccessful Registrations

6.2.1 If either the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

6.2.2 In the unlikely event that the ACR web registration site is not accessible, participating sites may still register a patient by faxing the completed eligibility checklist to the DMC at the ACR (215-717-0936, ATT: PATIENT REGISTRATION). ACR staff will fax a response to the registering site with the confirmation of registration and patient case number as soon as possible.

7.0 DATA COLLECTION AND MANAGEMENT

7.1 General

7.1.1 The ACRIN web address is www.acrin.org

7.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (*BDMC*) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (*BC*) is located at Center for Statistical Sciences in Providence, RI, and the Data Management Center (*DMC*) is located at the American College of Radiology's Data Management Department in Philadelphia.

7.1.3 The BDMC uses screens on the ACRIN web site to register patients, collect patient data, and maintain calendars of data submissions for each patient. By using the World Wide Web, ACRIN has made patient registration, data entry, and updated calendar information available to clinical sites 24 hours a day.

7.2 Clinical Data Submission

7.2.1 As soon as a patient has been registered, the RA may download the patient's data submission calendar, which lists all forms and/or designated reports required by protocol, along with the date that each form is due at the DMC. These calendars will be updated as the study proceeds to reflect data that has been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events or changes in the protocol which might change the data being collected or their timing. Updated calendars for each patient can be obtained 24 hours a day from the ACRIN website.

- 7.2.2** An investigator is obliged to submit data according to protocol as detailed on each patient's calendar as long as the patient is alive and the case status is designated as open or until the study is terminated. The case is closed when all data have been received, reviewed and no outstanding query exists for the case.
- 7.2.3** To submit data via the ACRIN website, the RA or investigator logs onto the web site, and supplies the preassigned user name and password. Case report forms will be available on the web site through a series of links. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the case report form, various logic checks will be performed. These logic checks look for missing data, data that is out of range, and data that is on the wrong form (*e.g. character data in a field requiring numeric responses*). Such errors will be detected as soon as the user attempts to either submit the form or to move to the next page. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered passes these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The data is transferred to the DMC and held.
- 7.2.4** Once a form is complete, the investigator presses the SUBMIT button on the patient calendar and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. An e-mail is generated and sent to the site listing all of the data completed and just submitted. Should a problem occur during transmission, this automated response supplies an explanation and instructions for resubmitting the data.
- 7.2.5** If a temporary problem prevents access to the Internet, investigators should wait until access is restored to submit data. Investigators should notify the DMC of the problem and the DMC will give an estimated time when access is expected to be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (**ISP**). On a short-term basis, the ACR can serve as an ISP.

7.3 Data Security

The registration system has built-in security features which encrypts all data for transmission in both directions preventing unauthorized access to confidential patient information. Access to the system will be controlled by a sequence of identification codes and passwords.

7.4 Electronic Data Management

- 7.4.1** Data received from the web-based forms is electronically stamped with the date and time of receipt by the ACRIN server. The data is then entered into the database. A variable in the new record is set to "Unreviewed," until the data is reviewed at the DMC. A validation program is used to perform more extensive data checks such as for accuracy and completeness. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. This validation program produces a log of errors which is sent

to the research associate for resolution. This program is frequently updated to incorporate exceptions to rules so that subsequent, correctly entered data pass validity checks, minimizing the time the DMC research associate at the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution.

- 7.4.2** If the program detects missing or problematic data, the DMC RA will send a Request for Information (*query letter*) to the investigator specifying the problem and requesting clarification. The DMC RA then updates the patient's data submission calendar with the due date for the investigator's response.

7.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, institutions are periodically prompted for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the U.S. mail system directly to both the RA and the investigator at each site, this report lists data items that are delinquent and those that will come due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the investigator.

7.6 Data Quality Monitoring

- 7.6.1** The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing interim analyses. These data will be drawn directly from the DMC's permanent database using a PowerBuilder utility that allows BC staff to log onto the DMC computer and select needed data. This analysis database will be maintained in permanent SAS (*Statistical Analysis System software*) format on the BC's ACRIN server and updated on a scheduled basis, usually monthly once the study is in its steady state. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.
- 7.6.2** A major goal of the monitoring of data in the BC is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data, which appear to arise from causes specific to an institution, the BDMC will apprise the site of the problem and work with the site until the problem has been resolved. If the BDMC cannot find a solution, the problem will be brought to the Executive Committee for further discussion and resolution.
- 7.6.3** The BC, in conjunction with the DMC, will prepare frequent summaries of the accrued data to be presented to investigators. These summaries will report accrual rates (*overall and by sub-groups of interest to the investigators*); assess the completeness and accuracy of the data; and discuss any trends that may impact the outcomes of the trial. These intermittent summaries will not include analyses of the study's endpoints. Only planned interim analyses will be performed.

8.0 DATA COLLECTION FORMS

8.1 Data Collection Table

| Form/Image Submission | | Submission Time Table |
|------------------------------|---|---|
| QP | MPAC | Pre-RFA for 5 days, post-RFA daily for 14 days, 1 month, and 3 months post-RFA. |
| I1 | Initial Evaluation/On-Study Form [±] | Within 2 weeks of study entry |
| TF | RFA Treatment Form | Within 2 weeks of RFA Treatment |
| F1 | Follow-Up Form [±] | At 1 week, 1 month, and 3 months post RFA |
| C1 | Pre-Treatment Imaging* (CT or MRI) (*baseline and pre-RFA if applicable) | 1 week post study entry |
| C2 | Follow-Up Imaging ([±] CT or MRI) | At 1 month and 3 months post RFA |
| C3/ME | Dictated Imaging Report (*for baseline and pre-RFA CT or MRI) | At 1 week post study entry |
| QC | Quality Control of All Images | Specified by study PI |

[±] Appendix VIII and IX should be referenced for forms completion.

8.2 Data Collection Submission

Send reports requested to:

**American College of Radiology
ACRIN 6661
1818 Market Street
Suite 1600
Philadelphia, PA. 19103
Fax: 215-717-0936**

Please contact the coordinating Data Manager for ACRIN 6661 at (215) 574-3150 regarding forms or data submission questions.

8.3 Image Submission

- 8.3.1** Digitally generated and scanned film diagnostic images can be transmitted to the ACRIN Data Management Center (*DMC*) via FTP directly to the image archive. The FTP site is located at <ftp://xray.acrin.org> or <ftp://206.137.103.34>. For each transmission a new folder for your institution and sub-folders for each corresponding exam must be created. Images are then to be transferred into those folders. An e-mail verifying the transfer and its contents including the name and number of exams as well as image count for each should be sent to both (*amurray@phila.acr.org*) and (*alevering@phila.acr.org*). Please verify the transmission by examining the folders to make certain that all the images were received.
- 8.3.2** Please note that the header record on DICOM formatted image data, which often contains information identifying the patient by name, MUST be scrubbed before the image is transferred. This involves replacing the Patient Name tag with the Institution ID or number, replacing Patient ID tag with the ACRIN case number and put the study number into the Other Patient ID tag. This can either be done by software present at the institution or software, which is available from the ACRIN DMC (*please contact Rex Welsh 215-574-3215 for information*).
- 8.3.3** In the event that either DICOM capability or transfer of scrubbed image headers is not available images may also be sent on a CD or other electronic medium for the ACRIN DMC to transfer to the image archive. Please contact the ACRIN DMC prior to sending the media to confirm compatibility.
- 8.3.4** Where applicable, plain film images may be sent via mail for digitization and subsequent entry to the image archive. All media and film will be retained by the ACRIN DMC unless otherwise requested and return packaging and postage is provided. Mailed screen-film images or images on CD should be addressed and sent as follows:

**ACRIN Image Archive
ACRIN 6661 Images
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA. 19103**

- 8.3.5** Images stored on the ACRIN DMC image archive will then be routed to other sites involved using either FTP or CD-ROM where appropriate for purposes of secondary interpretation.

9.0 TREATMENT PLAN

9.1 RFA EQUIPMENT

A Radionics CC-1 (*Radionics Inc, Burlington, Mass*) radiofrequency generator and perfusion pump will be used. A Radionics single 17 gauge or cluster Cool-tip electrode (*Radionics Inc, Burlington, Mass*) with variable lengths (*15,20cm*) and tip exposure (*1-3cm single; 2.5cm cluster*) will be used.

- 9.1.1** RFA will be performed under conscious sedation (intravenous midazolam and fentanyl or reasonable alternative based on institutional preference). General endotracheal or laryngeal mask anesthesia will not be allowed for ablations in proximity to a neurovascular bundle supplying an extremity or in the spine, since sensorimotor testing must be performed. However, general anesthesia may be performed at a site where the nerve injury is not of clinical concern, especially if it is requested by the study participant and/or determined it is in the best interest of the participant to use general anesthesia. Patients will be monitored with continuous pulse oximetry, and EKG with blood pressure performed every 5 minutes. Computerized tomography will be used to localize the metastasis. Standard surgical prepping and draping will be performed. Local anesthesia will include 1% lidocaine both intradermally and around the periosteum. A 14-gauge coaxial bone biopsy needle (*Ackerman*) will be placed into the lesion if the cortical bone is intact. After the core is removed the inner trephine needle will then be removed, and the RF electrode will then be placed through the outer cannula into the metastasis. In cases with larger tumors that have destroyed the bone cortex, the RF electrode can be placed directly into the metastasis. Tumors over 4cm in size will be treated with a cluster RF electrode consisting of three 17-gauge needles spaced 5mm apart. Tumors smaller than 4cm will be treated with a single RF electrode. Single RF electrodes come in 1, 2 or 3cm active tip lengths. Tumors smaller than 2cm will be treated with a 1cm active tip, tumors between 2 and 3cm will be treated with a 2cm active tip and tumors 3-4cm will be treated with a 3cm active tip length. When possible the RF electrode should be positioned with the electrode shaft parallel to the longitudinal axis of the tumor. The tip of the RF electrode will be positioned against the deepest margin of the tumor. This treatment strategy will allow the optimal heat distribution for any given tumor. Axial and craniocaudal placement of the RF electrode will be confirmed with CT. In patients with spinal metastases the vertebral body cortex between the mass and the spinal canal and exiting nerve root must be intact. An intact cortex will help prevent thermal toxicity to the spinal cord and nerve roots. The site principal investigators will be responsible for determining eligibility based upon the initial CT or MRI examination.

The radiofrequency electrode contains an internal thermistor for temperature measurement. The electrode will be coupled to a Radionics CC-1 radiofrequency generator and perfusion pump. (*Radionics Inc, Burlington, MA*) Internal cooling of the electrode (*tip temperature 10-20° C*) will be performed with continuous infusion of ice water at 80ml/min with the accompanying perfusion pump. At the end of each treatment the perfusion will be stopped and the maximum temperature recorded. The quantity of RF energy cannot be standardized for each individual tumor because the heat capacity of

any given tumor may vary based on tumor histology, local blood flow and previous treatments. At least one RF treatment will be created with the maximal allowable current given the impedance of the system (*typical range 1100-1600mA*) for a time of no greater than 4 minutes. After the 4 minute period the internal perfusion of the electrode will be stopped and the current will be turned off. The maximal intratumoral temperature will be recorded. An intra-tumoral temperature greater than 60° C must be obtained to insure adequate thermocoagulation. If the temperature exceeds 60°C the RF electrode will be withdrawn in increments of 1cm up to the length of the active tip (*e.g. three 1cm increments for a 3cm active tip single electrode or 3cm for a 2.5cm active tip cluster electrode*) while measuring the intratumoral temperature. If the temperature falls below 60° C. and the RF electrode is still within the tumor mass as determined by imaging, then another 4min treatment will be performed at the new position. If after the first 4min treatment the maximum intratumoral temperature does not exceed 60° C, then an additional 4min treatment will be performed at the same position. This can be repeated for a maximum time of 12min (*i.e. 3 treatments*) at any given electrode position. After the entire longitudinal dimension of the tumor is treated with a series of overlapping temperature-based treatments the RF electrode is positioned into a new portion of tumor such that the electrode shaft is 1.5-2cm away from the longitudinal axis of the previous series of treatments. This is repeated until these cylinder-shaped treatment regions have encompassed the volume of the tumor mass. A single 12 min heat lesion with a cluster electrode can create a diameter of thermocoagulation of approximately 7.0cm³ depending upon regional tissue perfusion. The utilization of shorter treatment times will prevent over-treatment of a given tumor, thus minimizing damage to adjacent normal tissues. The treatment current in milliamps, power in watts, impedance in ohms as well as duration and maximal intratumoral temperature for each treatment will be recorded. The electric current is grounded by applying four grounding pads (*in the horizontal configuration*) (1800cc³/each) to the anterior and posterior aspect of the patient's thighs. If an extremity is to be treated the pads will be placed on the anterior and posterior torso. Proper coupling of the gel to the patient's skin may require shaving of body hair in the region where the pad is to be applied. If an adjacent neurovascular bundle is within 3cm of the electrode tip continuous assessment of the nerve function is obtained by motor testing. This is accomplished by instructing the patient to extend and flex the extremity supplied by the adjacent neurovascular bundle during the lesion generation. If the patient cannot do the instructed tasks then lesion generation cannot be performed or must be stopped. Major vessel heating is minimal due to the cooling effect of flowing blood that acts as a heat sink. Including patients with tumors 8cm or smaller, and treating spinal metastases that have an intact vertebral body cortex will allow the study to accrue patients who would typically present with poorly controlled pain. Excluding all spinal metastases and treating only smaller tumors would prevent adequate patient accrual because it is unusual for cancer patients to have poorly controlled pain relief with small tumors and many cancer patients have spinal metastases given this common site of spread given the presence of the hematopoietic marrow. Weight bearing bones of the lower extremity will not be treated due to the risk of pathological fracture. Apart from having performed 10 image-guided bone biopsies and 10 RFA procedures, no additional credential or supervision is necessary.

Post RFA procedure, patients vital signs are to be monitored for a minimum of 2 hours.

9.2 Assessment of Pain

Pain will be assessed using the MPAC as shown in Appendix V. There are three 100 mm-long lines printed for visual analogue self assessment scales measuring intensity of pain (*VASPI*), mood (*VASMOOD*) and pain relief (*VASPR*). The patient is asked to place a mark along the line to indicate his or her judgment of pain intensity, mood and pain relief. The score is obtained by measuring in millimeters the distance between the left end of the line and the patient's mark. The MPAC also includes a categorical verbal rating scale of pain severity (*Tursky scale*), which is scored from 1 (*no pain*) to 10 (*excruciating pain*). The pain cards take less than 60 seconds to complete. The MPAC forms are to be completed by the patient during the pre-RFA time period for 5 days before RFA, after RFA daily for 14 days, and at 1 month and 3 month follow-up visits. If the patient is not capable of returning for one of the required follow-up visits, the MPAC forms may be mailed with written instructions for completion. Included with the MPAC forms and instruction should be a stamped returned envelope. The MPAC forms will be kept on site at the participating institution and the measurement will be entered on the case report form and submitted to the DMC. If there is no measurable improvement in at least one of the four pain scales at 1 month, the patient may have systemic or other local treatment of the metastasis.

10.0 TOXICITIES OF RFA

The most common risks of the procedure are potential bleeding, infection and tissue damage related to the biopsy needle placement. Bleeding is a rare complication using this technique since the procedure involves tissue thermocoagulation. Pre-procedural coagulation studies are required to identify potential bleeding diatheses.

Rare individual risks of RFA relate to the proximity of neighboring structures and their potential damage by RFA. These will be discussed individually with the patient.

If a heat lesion is in close proximity to a major motor nerve, the possibility of nerve damage due to heating will be discussed with the patient before hand. This damage will be minimized by continuous motor nerve monitoring during the procedure.

11.0 TESTS AND OBSERVATIONS

| | Baseline (to determine eligibility) | Pre RFA | 1 week post RFA (8-10 days) | 1 month (26-33 days) | 3month (83-97 days) |
|-------------------------|--|--------------------|--|---------------------------------|--------------------------------|
| General | | | | | |
| History/Physical | X | X | X | X | X |
| Signed Informed Consent | X | | | | |
| ECOG Performance Status | | X | X | X | X |
| | | | | | |
| Laboratory | | | | | |
| CBC, DIFF, PLT | X ^b | | X | | |
| PT, PTT | X ^b | | | | |
| NA, K, BUN, CR, CA | X ^b | | X | | |
| | | | | | |
| Imaging | | | | | |
| MRI or CT | X ^a | | | X | X |
| | | | | | |
| Pain Assessment | | | | | |
| MPAC | X | X ^c | X ^c | X | X |

- a. within 60 days prior to RFA
- b. within 14 days of RFA
- c. To be completed 5 consecutive days prior to RFA and 14 consecutive days post-RFA.

11.1 Quality Control of Images

Quality Control will be established to monitor compliance to protocol specifications. The Principal Investigator will review all studies from all institutions. The studies will be analyzed for four quality control measures: adequacy of contrast administration, proper field of view, slice thickness and coverage of tumor, lack of patient motion and proper window and level display. This will allow deviations from protocol to be discovered at the earliest possible time. Studies that do not meet quality standards will result in notification by the Principal Investigator of the study to the institutional site radiologist. The site will be asked to submit plans to rectify any systematic problem.

11.2 Follow-up Studies

11.2.1 General

MPAC will be obtained daily for 14 days post RFA, at one month, and three months. History and performance status will be obtained at 1 week, one month, and three months. Adverse events should be reported at all of the follow-up visits. Chemotherapy will not be allowed to be given until 14 days after the RF procedure.

11.2.2 Laboratory

Complete blood count, blood urea nitrogen, creatine, potassium, and calcium will be obtained at one week.

11.2.3 Diagnostic

Contrast-enhanced CT and/or MRI (*Helical CT or high field ≥ 1.0 Tesla MRI*) will be performed at one and three months. The follow-up image modality should be the same type as the pre-treatment imaging.

11.2.3.1 CT will be performed with the following protocol. After a digital scout localizer of the affected region an appropriate field of view will be chosen to include at least the entire affected region. CT images will be obtained with 5mm thick collimation 1 minute after and during the intravenous infusion of 130cc 60% nonionic, iodinated contrast media by power injector at 1ml/sec. The CT sections will be filmed in standard bone (*e.g. window width +2000 Hounsfield units(HU); window level +350HU*) and soft tissue (*e.g. window width +500 HU; window level +50HU*) windows. 750ml of dilute oral contrast will be administered three–four hours prior to scanning when a metastasis is known to be near to hollow viscera.

11.2.3.2 MRI examination will be performed according to the following parameters. A rapid low-resolution localizer sequence will be used to identify the region of interest. Then, using a local coil for extremity or body coil for pelvis, hip, chest wall or spine, axial and longitudinal T1-weighted sequences (*TR 300-600msec; TE 10-20msec*) will be obtained before and at least 5 minutes after the intravenous administration of approximately 10cc gadolinium contrast. Fat saturation will be performed for the T1-weighted post-gadolinium images. The slice thickness will be no larger than 5mm with no more than a 1mm gap between slices. The number of phase–encoding steps will be 192-256 with at least two excitations. Axial and longitudinal Fast-spin echo T2-weighted images (*TR/TE 2000-3000msec/ 30-80msec*) images will also be obtained. The number of phase-encoding steps will be 192-256 with at least two excitations. Tumor size (*cm*) and size of thermocoagulation (*cm*) will be measured in three axes. The size of thermocoagulation (*cm*) will be determined by the measurement of the non-enhancing portion within the tumor mass. Sites may elect to perform STIR instead of a T2 for extremities. See Appendix X for imaging parameters. Known preexisting cystic areas will not be included in the measurement of thermocoagulation.

12.0 ADVERSE EVENT REPORTING

Investigators are required by Federal Regulation to report adverse events and reactions to RFA. The following AE guidelines apply to commercial agents and devices. Each site investigator will determine if the toxicity is treatment-related. Please refer to the ACRIN Adverse Event Reporting Manual for more specific details about what to report and when. Anyone uncertain about whether a particular adverse event should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance.

The revised NCI Common Terminology Criteria Adverse Events (*CTCAE*) version 3.0 (7/03) must be used to score event severity. The CTCAE version 3.0 and the CTC search tool are available on the CTEP web page (<http://ctep.info.nih.gov>).

12.1 An Adverse Event (AE) with the attribution (*possibly related, probably related or definitely related*) must be reported. Adverse Events of less severity are reported on case report forms and submitted with routine data submission; however, the following guidelines require a written report submitted within 10 days of the event.

12.1.1 Any adverse event (AE) that is both serious (*life threatening, fatal*) and unexpected. This may include but is not limited to the following: hemorrhage which results in a significant drop in blood pressure (<90mmHg systolic) that is identified on imaging; infection documented by isolated organism at RFA site or blood cultures.

12.1.2 Any **increased** incidence of a **known or expected** AE that has been reported in the literature, in package inserts or in the consent form. This may include, but is not limited to the following: local pain; referred pain; or grounding pad burn.

12.1.3 Any **death on study or within 30 days** of completion of RFA, regardless of attribution and whether the event was expected or unexpected (see section 12.2.3).

12.2 How to Report

12.2.1 An expedited adverse event report requires submission to the NCI's Biomedical Imaging Program and ACRIN using the paper templates "Adverse Event Expedited Report—Single Agent" or "Adverse Event Expedited Report—Multiple Agents," available on the CTEP home page, <http://ctep.info.nih.org>.

12.2.2 Completed expedited reports should be sent to:

NCI
Barbara A. Galen, MSN, CRNP, Program Director
Re: Adverse Event Report
Biomedical Imaging Program
6130 Executive Blvd., MSC 7412
Room 6050
Bethesda, MD 20892-7412

To make a telephone report, contact NCI-CIP at 301-496-0737, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM E.S.T.).

12.2.3 A copy of all expedited adverse event reports should be sent to ACRIN by fax at 215-717-0936. All fatal adverse events should be reported by telephone within 24 hours of the event. To make a telephone report to ACRIN, call 215-717-2763, available 24 hours a day (recorder after hours from 5 PM to 9AM E.S.T.; specify that you are reporting an adverse event). You should also notify the ACRIN group chair and the study Principal Investigator (see cover sheet for contact information).

- 12.3** Submission of documentation of adverse events to individual site institutional Review Boards should follow institutional requirements; however, the above specified guidelines should be followed for ACRIN reporting, i.e., IRB guidelines may require reporting of **unrelated** adverse events that are not reported to ACRIN. All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events not requiring expedited reported are normally reported to your local IRB in an annual report.
- 12.4** Events that require telephone reporting must be followed within 10 days by the written report as described above. The site investigator may be requested to submit a dictated note with details of the event. Data forms are due as specified above.
- 12.5** This study will be monitored by the Clinical Data Update System (*CDUS*). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.0 STATISTICAL CONSIDERATIONS

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14.0 INSTITUTIONAL AUDITS

- 14.1** Institutional on-site audits will be completed within 18 months of a site's enrolling its first ACRIN participant. Subsequent audits will be scheduled per the outcome of the initial audit. Auditors will follow procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparing for the audit will be sent to sites in advance of the audit date. With these instructions, the auditors will specify which case records will be reviewed during the audit. Auditors will review on-site records against the reviewed data, and they will record their findings on specially prepared questionnaires. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will be also reviewed at the audit.
- 14.2** To help sites prepare for audits and assure that clinical RAs maintain records appropriately, ACRIN staff will offer training. This training will cover all aspects of data collection, but will include special instructions for finding and filing the kinds of source documentation needed to verify the accuracy of submitted data for this trial.
- 14.3** **Source documentation**: Data elements that are expected to be extracted from the medical record (patient history, official clinical interpretations of images, pathology or surgery results) and recorded on the case report forms (CRFs) will be audited against the appropriate component of the medical record. Data elements gathered from signed patient questionnaires may be documented on the CRF. The image interpretation data beyond that documented in the radiology report may be recorded on the CRF and is accepted as source documentation if signed by the MD. At the time of audit, the auditor

will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (patient questionnaire, CT, MR, etc.). Section 14.7 includes a listing of study-specific forms and the source documentation that will be accepted at the time of the audit. Any use of CRFs as source documentation where it is designated the information will be audited against the medical record will be considered a discrepancy.

14.4 Institutional Review Board: Sites must have on hand documentation of IRB approval prior to subject registration, including a copy of IRB approval of initial application, a copy of IRB approval of modifications, and copies of annual renewal(s).

14.5 Equipment Safety or Service Reports:

MR and CT Scanners: Obtain copies of *MRI and CT Preventive Maintenance Reports* for the previous 18 months or the duration of the study (whichever is less) for review at the time of the audit. Preventive maintenance is usually performed at least once every 3 months by the scanner manufacturer's service engineer and reports may be maintained by the facility or the manufacturer. Sites must have MR and CT Preventive Maintenance Reports documenting quarterly service.

14.6 Research Records: Maintain *source documentation* for each case that substantiates the data reported to ACRIN.

Source documentation can include the following:

- hospital chart or legible copies
- clinic chart or legible copies
- treatment reports
- pathology reports
- MRI reports or legible copies
- CT reports or legible copies
- RFA procedure reports
- physician/nurse notes
- forms signed and dated by the subject
- ACRIN case report forms signed by the physician
- worksheets signed by the physician which are used by research staff to submit the data on case report form(s)
- verification of receipt of submitted case report forms (mailed or emailed from ACRIN to site)

Source documentation must verify the eligibility criteria and data submitted on all case reporting forms. If an item is *not mentioned* (e.g., history and physical with no mention of a psychological condition) it will be assumed it is *not present*.

It is suggested that the research record for each case contain copies of the source documentation for the data reported to ACRIN. Copy the source documentation as you abstract the data from the primary record. This will prevent a discrepancy and inability to document the data reported when reviewed by auditors.

14.7 Source Documentation for Audit

| Form | | Data Collection / Time of Submission | Source Documentation |
|-----------|---|---|--|
| A0 | Registration | (SC)- Eligibility checklist must be completed prior to web registration. (A0) At time of registration via the ACRIN web site. | SC - Eligibility checklist completed signed and dated by RA or MD. and/or A0 - Completed, signed and dated by RA, after signed consent. |
| I1 | Initial Evaluation Also known as on study form | Due within two weeks of registration | Lab report(s) Pathology report(s) MRI /CT report(s)** Participant History and Physical (H &P) MPACS documented by the MD and/or a medication log Physician progress notes and I1 - Completed, signed and dated by RA or MD*** |
| TF | RFA Treatment Form | Due post RFA procedure. | RFA procedure report (radiology) and/or Procedure notes (signed and dated by MD/Nurse) and/or TF form - signed and dated by MD*** |
| QP | MPAC Results Form | This form (QP), completed by the RA, records the MPAC results that are completed by the Participant. Only the QP gets submitted to ACRIN. The MPACS or pain scales stay at the site. Due: 5 days prior to RFA procedure 14 days post RFA procedure 1 month post RFA procedure 3 months post RFA procedure | The MPACS form(s) completed by the Participant are the source document(s) for the QP form(s). and QP form(s) completed, signed and dated by the RA. |
| F1 | Follow-Up Form | There are 3 scheduled follow-up periods. Participant is to complete the DP – Patient Pain Medication Diary Worksheet x3 (daily for one week prior to RFA, and for two weeks after RFA) | Lab report(s) MRI /CT report(s)** Participant History and Physical (H & P) Physician progress notes and/or Treatment notes (including any reported toxicities) DP completed signed and dated by the Participant. (3 pages) and F1 - Completed, signed and dated by the RA. |

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APPENDIX I

ACRIN 6661

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE:

A PHASE I/II STUDY OF PERCUTANEOUS RADIOFREQUENCY ABLATION OF BONE METASTASES USING CT GUIDANCE

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The American College of Radiology Imaging Network sponsors this trial.

The researcher will first explain the project and then ask you to participate. You will be asked to sign this agreement, which states that the project has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the project. He or she will explain how the project will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the project. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

You are being asked to be in this study because you have a bone metastasis. This means that your cancer has spread to your bone(s).

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) the procedure radiofrequency ablation has on the pain that you have from the spread of cancer to your bone(s).

Radiofrequency is a type of electrical energy that uses radio waves to cause heating. This heat can kill cancer cells and normal tissue in a small-defined area. Radiofrequency ablation is the destruction of cells through the use of heat.

This research is being done to see if radiofrequency ablation helps reduce the amount of pain from your bone metastasis.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 75 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following tests and procedures:

Schedule

Prior to Radiofrequency Ablation

Procedure

Physical exam with a medical history.

Blood tests- (about 3 teaspoons) (to include a CBC, blood clotting tests called PT and PTT, and blood chemistries.)

MRI or CT scan of the area of the bone metastasis.

For 5 days before the radiofrequency ablation procedure, you will also be asked to complete 4 brief questionnaires regarding your pain and mood as your pain affects it.

Radiofrequency Ablation Procedure

The Radiofrequency Ablation will be done as an outpatient at your institution. Your doctor will discuss with you how your metastasis will be treated, depending on its size, location and symptoms.

On the day of your radiofrequency treatment an intravenous (an IV tube that goes into your vein) will be placed. You will be given sedation and medicines through your IV to reduce any discomfort you may have during the procedure. You will be required to lie still on your stomach or back for approximately 60 minutes during the treatment. You will be placed in the MRI (a specialized machine that uses radio waves to take computerized images of the body) or CT scan machine (a specialized X-ray machine that takes computerized images of the body). At the site of your metastasis, your skin will be cleaned and draped in a sterile fashion to reduce the risk of infection. You will be given injections of a “numbing” medicine at the site to reduce any discomfort you may have with the needle placement. With MRI or CT scan guidance a needle will be placed directly into the bone metastasis. Then using the needle as a guide, an electrode will be placed into the metastasis. Pads, used as a “ground”, will be placed on your thighs, chest or back. The electrode will be attached to a radiofrequency generator. The metastasis will be treated with radiofrequency heat for approximately 12 minutes. A large metastasis may need more than one treatment to be done at the same time. Immediately following the procedure you will be required to remain in the hospital for two hours. You will be monitored for pain and recovery from the sedation that you received during the procedure. After approximately two hours, and once it has been determined that you have recovered from the sedation, you will be allowed to leave the hospital. Because we will be measuring the intensity of pain after the procedure, you will be asked not to have any therapy with radioisotopes to the area that was treated by the RF ablation for 30 days. You will be asked not to have chemotherapy for 14 days.

One Week after Procedure:

Blood tests (to include a CBC and blood chemistries).

For 14 Days after the Procedure: Complete 4 brief questionnaires each day regarding your pain and your mood as affected by your pain.

At All Follow-up Appointments: Physical exam with a medical history.
(1 month and 3 months after the Radiofrequency Ablation)

Complete 4 brief questionnaires regarding your pain and mood as your pain affects it and about the amount of pain medication you are taking.
Blood tests

MRI or CT Scan of the area that was treated.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for 3 months. Your follow-up appointments will be at one week, one month, and three months after the radiofrequency ablation procedure.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the Radiofrequency is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with Radiofrequency Ablation Treatment:

Pain at the injection site - "Numbing" medicine will be used around the area to be treated. I.V. medicines will be used for additional pain control. If you and your doctor elect to use sedation (general anesthesia) with the procedure, the risks of using sedation will be reviewed with you in separate consent by the anesthesiologist.

The pain may be worsened with the procedure or weakness and numbness may result if a nerve is within the vicinity of the RF treatment.

Bleeding – is a rare complication using this technique. Blood tests to check clotting time will be done prior to the procedure. Aspirin and nonsteroidal anti-inflammatory, low molecular weight heparin or antiplatelet medications should be stopped at least 7 days before having the procedure.

Infection – This procedure causes tissue to die and as a result there is an increased risk of infection.

Tissue damage related to the biopsy needle placement – Tissue damage or nerve damage related to needle placement or RF lesion production is minimized by using image (CT or MRI) guidance to ensure that the needle and RF electrode are in the appropriate position. There is the risk, that if the RF electrode is positioned within the spinal column to treat a tumor, heat from the procedure may cause nerve damage (causing numbness and/or weakness). Again however, image guidance will be used to ensure that the electrode is placed appropriately, avoiding the risk of nerve injury.

Bone fracture – Bone fracture from the needle placement may occur because of the existing bone cancer.

Risks Associated with the CT and MR Imaging Studies

In order to better distinguish healthy tissues(s) from disease on the CT or MRI, an intravenous (IV) contrast agent will be used. The contrast agent (dye) used in CT, although very safe, has been associated with allergic reactions. Allergic reactions to these types of contrast agents are rare and most are mild, but some can be life threatening. Every effort will be made to screen you for allergies before an agent is given. Even more rare than CT contrast reactions, are those associated with the MR contrast agent. The MR contrast agent, Gadolinium is also very safe. If you experience an allergic reaction, with the CT or MRI contrast agent, you will be treated for the reaction. If you have allergies or have had an allergic reaction to contrast in the past, please notify the researcher explaining this form.

In addition, some patients feel discomfort from being in a CT/MRI machine.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with bone metastasis in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy, (2) chemotherapy, or (3) no treatment except medication to make you feel better. These treatments could be given alone or in combination with each other.

Your doctor can tell you more and the possible benefits of the different available treatments. Please talk to your doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN). Your personal information may be disclosed if required by law.

Copies of your CT or MRI films will be permanently kept on file at ACRIN. This information will be used for research purposes only. All identifiers will be stripped off of the films to maintain confidentiality. Additional studies may be done using the data we collect as part of this research project.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the National Cancer Institute (NCI), and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For additional information about your health, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

Visit the NCI's Web sites for comprehensive clinical trials information **<http://cancertrials.nci.nih.gov>** or the American College of Radiology Imaging Network's website **www.acrin.org**.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient Signature (*or legal Representative*)

Date



APPENDIX II
ACRIN Protocol Specific Application

ACRIN 6661
PERCUTANEOUS RADIOFREQUENCY ABLATION OF BONE METASTASES USING CT GUIDANCE

This application is in addition to the ACRIN General Qualifying Application which can be found on the ACRIN web page (www.acrin.org).

Name of Institution _____

ACRIN Radiofrequency Protocol P.I. Name _____

Address _____

Telephone _____ Fax _____ E-mail _____

Research Associate's Name _____

Has your institution identified a **credentialed** radiofrequency investigator? ___ Yes ___ No
(To be credentialed, the investigator must have previously performed at least 10 RF ablations with at least one with the Radionics device and have performed at least 10 CT guided biopsy procedures)

If yes, what is the Investigator's name _____

Address _____

Telephone _____ Fax _____ E-mail _____

Does your institution have a CT with helical/spiral capability? Yes ___ No ___

If yes, (Brand and Type) _____

Number of RF ablations previously performed (list # of procedures for each device) _____

Number of Bone RF ablations previously performed (list # of procedures for each device) _____

Number of complications associated with those Bone RF ablations _____

Signature of Credentialed Investigator _____ Date _____

Please submit application to:
ACRIN Administrator, Attn. 6661 PSA
ACRIN
1101 Market Street, Suite 1400 Philadelphia, PA 19107
Fax: 215-928-0153
Philadelphia, PA 19107

Institution # _____

APPENDIX III

ACRIN 6661

ELIGIBILITY CHECK (page 1 of 3)

Case # _____

(to be provided upon activation)

The following questions will be asked at Study Registration:

- _____ 1. Institutional person registering case (initials only)
- _____ (Y) 2. Have all of the questions on the Eligibility Checklist been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ (Y) 4. Date the study-specific Consent Form was signed? *(Must be prior to study entry)*
- _____ 5. Patient's Initials (Last, First)
- _____ 6. Verifying Physician (Site PI)
- _____ 7. Participant's ID number (Do NOT utilize a medical record number or radiology-assigned number)
- _____ 8. Date of Birth (mm-dd-yyyy)
- _____ 9. Ethnic category
- 1 Hispanic or Latino
 - 2 Not Hispanic or Latino
 - 9 Unknown
- _____ 10. Race
- 1 American Indian or Alaskan Native
 - 2 Asian
 - 3 Black or African American (not Latino)
 - 4 Native Hawaiian or other Pacific Islander
 - 5 White
 - 6 More than one race
 - 9 Unknown
- _____ 11. Gender
- 1 Male
 - 2 Female
- _____ 12. Patient's Country of Residence
- 1 United States
 - 2 Canada
 - 3 Other
 - 4 Unknown

ELIGIBILITY CHECK (page 2 of 3)

- _____ 13. Zip Code (US residents)
- _____ 14. Patient's Insurance Status
- 1 Private insurance
 - 2 Medicare
 - 3 Medicare and private insurance
 - 4 Medicaid
 - 5 Medicaid and Medicare
 - 6 Military or Veterans Administration
 - 7 Self-pay
 - 8 No means of payment
 - 9 Unknown/decline to answer
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date (mm-dd-yyyy)
- _____ 17. Other country of residence, specify:
- _____ 18. Treatment Start Date
- _____ 19. Registration Date
- _____ 20. Name of Medical Oncologist
- _____ (Y) 21. Bony metastases with a maximum size of < 8cm
- _____ (Y) 22. Documented metastatic bone disease from primary other than musculoskeletal malignancy, lymphoma or leukemia.
- _____ (6-10) 23. Persistent intractable pain as measured by the VASPI pain score on a 0-10 scale.
- _____ (Y) 24. Pain originates from a solitary site of bony metastatic disease.
- _____ (Y) 25. Radiofrequency treatment will be performed within 5 days of baseline evaluations.
- _____ (Y) 26. Platelets are $\geq 70,000/\text{ul}$.

ELIGIBILITY CHECK (page 3 of 3)

- _____ (N) 27. Previous or scheduled treatment of metastases with chemotherapy, external beam radiation, or radioisotopes within 30 days immediately prior to RFA treatment. (Chemotherapy will not be allowed until 14 days post procedure.)

- _____ (N) 28. Treatment site involves weight bearing long bone of the lower extremity.

- _____ (N) 29. Patient has a pacemaker.

- _____ (N) 30. Impending fracture or metallic fixation at RFA site.

- _____ (Y) 31. Baseline laboratory assessments as described in Section 11.0 performed within 14 days of the RFA.

- _____ (Y) 32. Discontinuation of medications in compliance with Section 4.2.3.

- _____ (N) 33. Is the treatment site located in the cervical, thoracic or lumbar spine?

- _____ (Y) 34. If spinal metastasis, is the vertebral body cortex between the mass and spinal cord/nerve roots intact?

Signature of person responsible for data: _____
Signature of person entering data onto the web: _____
Date form completed (mm-dd-yyyy): _____

APPENDIX IV

PARTICIPATING INSTITUTION LIST

Beth Israel -Deaconess Hospital

S. Nahum Goldberg, M.D., Radiology

Brown University

Damian Dupuy, M.D., Radiology

Thomas DePetrillo, M.D., Oncology

Thomas Jefferson University Hospital

Adam Zoga, M.D., Radiology

Wake Forest University Hospital,

Bowman Gray Campus

Ronald Zagoria, M.D., Radiology

William Blackstock, M.D., Radiation Oncology

Leon Lenchik, M.D., Musculoskeletal Radiology

Frank Torti, M.D., Medical Oncology

William Ward, M.D., Orthopedic Surgery

UC Davis

John McGahan, M.D.

Barnes Jewish Hospital

Daniel Brown, M.D.

University of Pennsylvania

S. William Stavropoulos, M.D.

MD Anderson

Kamran Ahrar, M.D.

University of Massachusetts

Sri Shankar, M.D.

University of Miami

Venkataramu Krishnamurthy, M.D.

University of Alabama

Robert Lopez, M.D.

St. Elizabeth's Health Center

Richard Barr, M.D.

Quantum Radiology

Gregory Smith, M.D.

Inova Fairfax Hospital

Alain Drooz, M.D.

Evanston Hospital

Tony Farrell, M.D.

University of South Alabama

Brad Steffler, M.D.

APPENDIX V

ACRIN 6661 MPAC INSTRUCTIONS

Instructions for Recording/Reporting Patient Self-Assessment (MPAC)

A cover page for each evaluation is completed for each time point whether evaluations are done or missed. Only the cover page is completed and submitted via the web as form type QP. To report results on the web data entry screen from assessments from linear analogue scales, results are reported as a single whole number value(s) for each evaluation.

Because results obtained using a linear analogue scale can be distorted if the scale undergoes duplication, e.g. photocopying, patients must record results only on original forms. Although an adequate number of original forms will be provided for each case registered, the institutional RA should request a small supply from the ACRIN registrar in advance of initial case registration.

Linear Analogue Administration

1. Provide the patient original MPAC forms only. The form is completed with a ballpoint pen. Do not allow the form to be completed with a wide nub pen, e.g., flair or pencil. (The MPAC form is to be completed by the patient, either in person or by mail. It cannot be done over the phone.)
2. Instruct the patient to place a vertical line that intersects the horizontal line at a point that represents his/her assessment.
3. Have the patient repeat this process for each linear analogue question. It is appropriate for the patient to make a mark at either end of the line, if this reflects his/her assessment. Review the results after the patient has completed the questionnaire to be sure that the line made by the patient touches some point on the horizontal line and to assure that each question was answered. The patient should sign the form.
4. Carefully check that the patient did not miss any item especially on the pre-treatment baseline evaluation as omissions can adversely affect analysis of results.
To obtain the value to be data entered for each item, measure using a standard metric millimeter ruler from the extreme left side of the line. Measure the length of the line in millimeters to the point it is intersected by the vertical line marked by the patient. The horizontal line measures 100 millimeters, therefore, the results will be a whole number between 0 and 100. This single whole number is reported as results for the question. This process is repeated for each linear analogue item.
5. Instruct the patient to note the time of evaluation completion for each MPAC completed. It will provide better quality data for analysis if the evaluations re completed at the same time each day. The completion times are then recorded on the QP form. The forms should be completed at the same time of day as the initial MPAC evaluation.

Other Points to Consider

See Appendix VI for patient instructions.

Surrogate results are unacceptable, i.e., the patient's spouse or a member of the patient's family cannot provide his/her interpretations of the patient's assessment.

If the patient requires assistance to complete the questionnaire departmental staff should provide this.

If the patient is not capable of returning for one of the required follow-up visits, the MPAC forms may be mailed with written instructions for completion. Included with the MPAC forms and instructions should be a stamped return envelope.

APPENDIX VI

ACRIN 6661 MPAC Patient Instructions

Instructions for Recording/Reporting Your Mood and Pain

You are being asked to complete the following forms so that we can assess your mood and pain and how it changes from day to day. You will be asked to complete these forms both before and after the RFA procedure. **You must complete these forms yourself. Do not have a friend or family member complete them for you.**

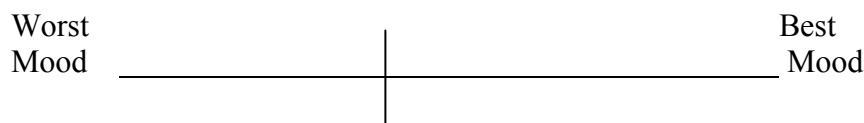
Please put the date and time that you are completing these forms on the top of every page. You should complete these forms at approximately the same time every day.

Please use only a ballpoint pen when completing these forms. Do not use a flair pen or pencil.

1. To complete tables 1, 2 and 3, please draw a line that describes how you are feeling. This line should intersect the line on the page at some point between each set of words. It is ok for you to mark at one end of the printed line if this best describes your mood or pain.

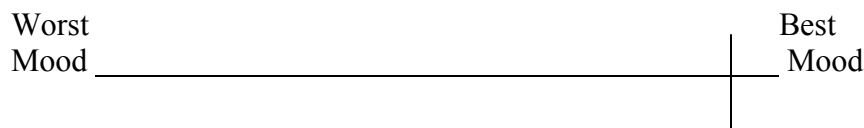
Example:

Mood



Or

Mood



2. For tables 4 and 5, please circle the answer that best describes how you have been feeling.
3. When you have completed the forms, please give them to the research staff. If these forms were mailed to you, please put them in the envelope that was provided and mail them to the research staff.

APPENDIX VII

ECOG PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction (*Karnofsky 90-100*).
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (*Karnofsky 70-80*).
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (*Karnofsky 50-60*).
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (*Karnofsky 30-40*).
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (*Karnofsky 10-20*).

KARNOFSKY PERFORMANCE SCALE

- 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 sign 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 personal needs
- 50 Requires considerable assistance and frequent medical care
- 40 Disabled; requires special care and assistance
- 30 Severely disabled; hospitalization is indicated, although death not imminent
- 20 Very sick; hospitalization necessary; active support treatment is necessary
- 10 Moribund; fatal processes progressing rapidly
- 0 Dead

APPENDIX VIII

PAIN AND NARCOTIC CATEGORIES AND SCORES

| PAIN | | ANALGESIA |
|--|--|---|
| S E V E R E I T Y | 0 - No pain | 0 - None |
| | 1 - Mild | 1 - Analgesics (<i>ASA, Bufferin, Tylenol, Anacin, etc.</i>) |
| | 2 - Moderate | 2 - Mild Narcotic, (<i>< 1/2 gr. codeine, Darvon, etc.</i>) |
| | 3 - Severe | 3- Moderate Narcotic (<i>> 1/2 < gr. codeine, Percodan, etc.</i>) |
| F R E Q U E N C Y | 4 - Constant (<i>most of the time</i>) | 4 - Strong Narcotic, (<i>> 1gr. codeine, demerol, morphine,</i> |
| | 0 - None | 0 - None |
| | 1 - Occasional (<i>< daily</i>) | 1 - p.r.n. (<i>< daily</i>) |
| | 2 - Intermittent (<i>at least daily</i>) | 2 - q.d. (<i>1 tab. or cap./day</i>) |
| | 3 - Frequent (<i>> 1 < 3 daily</i>) | 3 - b.i.d. t.i.d. (<i>> 1 < 4 tab. or cap./day</i>) |
| 4 - Constant (<i>most of the time</i>) | 4. - > t.i.d. (<i>> 4 tab. or cap./day</i>) | |

Pain Score = Pain Severity Grade x Pain Frequency Grade

Narcotic Score = Analgesia Severity Grade x Analgesic Frequency Grade

APPENDIX IX
Analgesic Conversion Tables

| <u>EQUIANALGESIC POTENCY CONVERSION</u> | | |
|--|--|--|
| <u>Name</u> | <u>Equianalgesic Dose (mg) po</u> | |
| Morphine | 60 | |
| Hydromorphone (<i>Dilaudid</i>) | 7.5 | |
| Methadone (<i>Dolophine</i>) | 20 | |
| Oxycodone | 30 | |
| Levorphanol (<i>Levo-Dromoran</i>) | 4 | |
| Codeine | 200 | |
| Vicodin | 60 | |

| <u>TRANSDERMAL FENTANYL (DURAGESIC) DOSE PRESCRIPTION</u> <u>based upon daily morphine equivalence</u> | |
|---|-------------------------------------|
| <u>Oral 24-hour morphine (mg/day)</u> | <u>Duragesic Dose (ug/h)</u> |
| 45-134 | 25 |
| 135-224 | 50 |
| 225-314 | 75 |
| 315-404 | 100 |
| 405-494 | 125 |
| 495-584 | 150 |
| 585-674 | 175 |
| 675-764 | 200 |
| 765-854 | 225 |
| 855-944 | 250 |
| 945-1034 | 275 |
| 1035-1124 | 300 |

| <u>NARCOTIC EQUIVALENCY INDEX</u> | | |
|--|---------------------|--|
| <u>NARCOTIC</u> | <u>ROUTE</u> | <u>CONVERSION FACTOR</u> |
| Morphine | IM/IV | 1.00 |
| | po | 0.17 for single dose trial; 0.33 for chronic administration |
| Hydromorphone (<i>Dilaudid</i>) | IM | 6.67 |
| | po | 1.33 |
| Codeine | IM | 0.08 |
| | po | 0.05 |
| Oxycodone* | IM | 0.67 |
| | po | 0.33 |
| Levorphanol (<i>Levodromoran</i>) | IM | 6.25 |
| | po | 3.13 |
| Meperidine (<i>Demerol</i>) | IM | 0.10 |
| | po | 0.03 |
| Methadone (<i>Dolophine</i>) | IM | 1.38 |
| | po | 0.69 |

* 1 tablet of Tylox, Percocet, or Percodan contains 5 mg of oxycodone.

APPENDIX X

CT/MR IMAGING PROTOCOLS

| Helical CT | |
|---------------------|---|
| CT Scout | Cover entire area to be imaged |
| Pitch | 1-4 |
| Slice Thickness | 5mm |
| Collimation | 1.25-5.0mm |
| IV Contrast | 130cc 60% non-ionic |
| Power injector rate | 1-2ml/sec 2-3min delay |
| Oral Contrast | 750ml 3-4 hours prior when imaging hollow viscera |
| Film: Soft Tissue | W+500, L+50 (HU) |
| Film: Bone | W+2000, L+350 (HU) |
| KVp | 120 |
| MA | 230 |

| MRI | | |
|--------------------------------|---------------------------------------|---|
| Magnet Strength | 1.0T-1.5T | |
| Coil | Extremity or Abdominal (Phased array) | |
| Fast Spin Echo (FSE) | Axial | TR=2000-3000msec, TE=30-80msec *may substitute Fast STIR for extremities |
| Fast STIR (extremities only) | Axial | TR=2000-3000msec, TE=30-80msec |
| Fast Spin Echo (FSE) | Long Axis (Sagittal or Coronal) | TR=2000-3000msec, TE=30-80msec Echo train =4-16 |
| T1 pre | Axial | TR=300-600msec, TE=10-20msec Slice thickness/spacing=5/1mm |
| T1 pre | Long Axis (Sagittal or Coronal) | TR=300-600msec, TE=10-20msec Slice thickness/spacing=5/1mm |
| T1 (5 minute) post | Axial + fat saturation | TR=300-600msec, TE=10-20msec Slice thickness/spacing=5/1mm |
| T1 (5 minute) post | Sagittal + fat saturation | TR=300-600msec, TE=10-20msec Slice thickness/spacing=5/1mm |
| Matrix (phase x frequency) | 192 x 256 for all sequences | |
| Gadolinium | Minimum 10cc | |
| Number of Excitations (NEX) | 2 for all sequences | |