A randomized trial evaluating rapid delivery of dose escalated Stereotactic Body Radiotherapy for patients diagnosed with bone metastases for effective palliation of symptoms.

1. OBJECTIVES:
    a. Primary objective: evaluate hypo-fractionated regimen for pain control in terms of time to failure, defined as the first occurrence of any of the following events:
        i. Worsening in pain score by at least 2 categories by MDASI survey,
        ii. ≥ 50% increase in dose of opioid/narcotic medication,
        iii. Re-irradiation,
        iv. Radiographic disease progression or development of pathologic fracture from disease progression
    b. Secondary objective: report outcomes
        i. Prospectively report pain, quality of life, and symptoms using MDASI assessment tool to measure pain response
        ii. Evaluate narcotics use after treatment
        iii. Report acute (skin, fatigue, flare reaction) and long term (sclerosis, bone ossification, bone fracture rate) toxicity associated with treatment.
        iv. Report local control, disease-free survival, overall survival
        v. Report rate of re-irradiation and salvage surgery

2. BACKGROUND:
    a. Radiation therapy is commonly utilized to effectively palliate symptomatic bone metastases, 50%-80% of patients experience improvement in the pain and 20%-50% report complete pain relief (1, 2). However, the optimal fractionation scheme to produce durable pain relief is still being studied. Historically, clinical trials have compared efficacy of varying dose-fractionation in alleviating symptoms. Ratanatharathorn et al. concluded in their analysis that higher dose fractionated treatments produced better pain outcomes compared to lower-dose regimens (3, Ratanatharathorn). Contrary to this, McQuay et al. in their summary determined no difference in efficacy between different fractionation or dose response in the total dose delivered for painful bone metastases (4, McQuay). In the meta-analysis performed by Wu et al (5, Wu) the authors compared pain relief among various dose-fractionation schedules of localized radiotherapy (RT) in the treatment of painful bone metastases. They concluded among the randomized trials, there was no significant difference in overall pain relief or dose response relationship between single and multi-fraction palliative RT for bone metastases.

    In the last two decades, multiple randomized trials have compared the efficacy of various dose-fractionation in achieving durable pain relief in patients diagnosed with bone metastases. A randomized trial, RTOG 9714 investigated whether 8 Gy delivered in a single fraction provided pain and narcotic relief

equivalent to the standard 30 Gy in 10 fractions. The study demonstrated both regimens were equivalent in terms of pain and narcotic relief, and well tolerated with few adverse effects. The shorter 8 Gy arm had a higher re-treatment rate but with less acute toxicity than the longer 30 Gy arm (6, Hartsell). However, the Trans-Tasman Radiation Oncology Group (TROG 96.05) was a randomized trial which demonstrated 8 Gy in a single fraction was not as effective as 20 Gy in 5 fractions; the overall response rate and time to treatment failure were inferior (7, Roos). The re-treatment rate has been reported to be higher in patients treated by single fraction radiotherapy; this could be due to the decrease in durability of pain response related to the lower dose equivalent (8, Sze).

A single delivery of higher dose of radiation treatment can be advantageous in regards to patient convenience and cost effectiveness as long as it can provide durable pain control. The optimal single fraction dose required to achieve pain control is still unknown and not determined from current clinical trials. Gaze et al demonstrated and overall pain response rate of 84% and complete pain response rate of 34% with delivery of a single fraction of 10 Gy (9, Gaze) for patients with osseous metastases. Higher doses of 12 Gy and 15 Gy have demonstrated a dose response of increased overall pain response of 86% and complete pain response in 57% of patients (10, Kagei). Radiosurgery doses of $\geq$16 Gy has been shown to increase the probability of pain relief for patients with spine metastases by multiple institutions such as Henry Ford and University of Pittsburgh (11, 12, Ryu, Gerzten). Researchers at M.D. Anderson have demonstrated the use of single fraction SBRT with doses of 16-24 Gy for spinal metastases was safe and allowed patients to achieve durable local control (88% at 18 months) with few toxicities (13, Garg).

Multiple prospective randomized trials have investigated the efficacy of shorter versus longer fractionated radiation therapy courses for the treatment of painful bone metastases with conflicting results. Few studies prospectively address the relief of neuropathic pain, re-irradiation rates, fracture rates and prospective quality of life endpoints. In this study, we propose to deliver a dose escalated single fraction (12 Gy or 16 Gy) regimen compared to the standard 30 Gy in 10 fractions to report the safest optimal hypo-fractionated regimen in providing durable symptomatic relief.

3. SCIENTIFIC RATIONALE:
    a. This study aims to prospectively evaluate the optimal radiation therapy dose to provide durable pain relief, assess patients' quality of life, narcotics use after radiation therapy, outcome, and toxicity. The goal of this prospective randomized trial is to radiate patients with mechanically stable, painful bone metastases effectively to provide quick palliation of pain. The hypothesis is rapid delivery of dose escalated hypofractionated radiotherapy for bone metastases effectively improves pain and results in durable pain control.

4. PATIENT ELIGIBILITY
    a. INCLUSION:
        i. Patients with a pathologic diagnosis of malignancy
        ii. Patients with any radiographic evidence of bone metastases, including plain x-ray, bone scan, CT scan, MRI, or PET scan
        iii. Patients with pain or dysathesia
        iv. Patients with a life expectancy of more than 3 months
        v. Patients able to complete pain assessment and quality of life surveys
        vi. Patients with multiple osseous sites are eligible; however should not treat more than 3 separate radiation treatment fields concurrently.
        vii. Patients with surgery for osseous metastases allowed.
    b. EXCLUSION:
        i. Patients with prior radiation therapy to the treatment site
        ii. Patients with a current, untreated spinal cord compression
        iii. Patients with a radiographic or pathologic fracture to the treatment site
        iv. Patients with painful metastases to hands and feet that need to be radiated on protocol
        v. Patients previously treated with radioactive isotope (e.g. Sr89) within 30 days of randomization

5. PRE-TREATMENT EVALUATION:
    a. The workup will include physical examination, radiographic evidence of metastases with either x-ray, bone scan, CT scan or MRI, and pathologic confirmation of malignancy per MDACC standard of care.
    b. All eligible patients will be enrolled after completion of the eligibility checklist.
    c. Use of pain medications (narcotic/opioids/NSAIDs) will be evaluated.

6. TREATMENT PLAN:
    a. Patients will be randomized to receive radiation therapy to:
        i. Arm 1: the standard hypofractionated regimen of 3 Gy x 10 fractions
        ii. Arm 2: 12 Gy x 1 fraction or 16 Gy x 1 fractions adaptively depending on the size of the metastases or gross tumor volume (GTV).
    b. Patients will undergo CT simulation and either 2-D or 3-D treatment planning for radiation therapy.
    c. Patients can be treated with 2-D, 3-D, or intensity modulated radiation therapy (IMRT)
    d. Patients will be treated with on board imaging (OBI) using KV, MV x-rays, cone beam CT or CT on rails per standard of care.
    e. Patients will be treated with 4-20 MV photon beam, 5-20 MeV electron beam, or 200 MeV-300 MeV proton beam.
    f. More than 1 osseous site may be included into one radiation treatment field.

7. EVALUATION DURING STUDY:

a. All patients will be evaluated by the radiation oncologist during radiation treatment
b. If surgical intervention is necessary, the patients will be evaluated by the treating surgeon
c. After start of treatment, all patients will be followed by phone calls within 7-14 days, and at + 1 month (+/- 1 week) and then with clinic visits at months 3, 6, 9, 12 (+/- 4 weeks for each visit) and every 3 to 6 month intervals thereafter (until death) by either the radiation oncology or orthopedic team to evaluate toxicity. The validated surveys (MDASI) will be completed at baseline prior to radiation and at each follow up interval/appointments. The patient medical record number will be placed on the survey before it is given to the patient for completion. The surveys may be filled out in person or by mail.
d. Patients will report their symptom measures with validated quality of life instrument MDASI index. The M.D. Anderson Symptom Inventory (MDASI) is a multi-symptom patient reported outcome measure evaluating 13 core symptom items interfering with patients' daily life (Appendix B).
e. We will also prospectively report the narcotics/NSAIDs utilization and outcome at each follow-up interval after radiation therapy.

8. EVALUATION OF TOXICITY:
   a. During radiotherapy, the patient will be examined weekly and acute reactions recorded.
   b. Toxicity occurring after 3 months of radiation therapy; these will be evaluated and documented using NCI CTCAE version 4.03 (Appendix A).

9. CRITERIA FOR RESPONSE:
   a. The response to treatment will be determined by both radiographic scans and symptoms reported.
   b. Complete pain relief is defined as average pain score of 0 for two consecutive analysis periods.
   c. The time to maximal relief of pain is defined from the first day of irradiation until the lowest pain score after radiation therapy.
   d. Treatment failure is defined as worsening of pain by at least two categories, >50% increase in dose of opioid/narcotic medications, re-irradiation for pain or disease progression, progression or development of pathologic fracture from disease progression.
   e. Any patient with progressive pain in the radiated area will have work up which include radiographic scans to evaluate for bone stability and pathologic fracture per standard of care.

10. RE-TREATMENT:
    a. Response and pain relief from radiation therapy may take several weeks; therefore patients should not be re-irradiated for at least 4 weeks after

completion of radiation. Dose and fractionation are left to the discretion of the treating radiation oncologist.

b. Surgical intervention for treatment failures, bone instability, or fractures will be reported.

11. STATISTICAL CONSIDERATIONS:

This is a phase II/III non-inferiority trial following the design suggestions of Korn et al. (14, Korn). The primary outcome for this study is treatment failure at 3 months, where treatment failure is as defined in section 1.0. We assume that time to treatment failure follows an exponential distribution for each treatment arm (standard radiation, hypofractionated radiation). We also assume that the standard radiation arm will have 25% of patients with treatment failure at 3 months, based on the study by the Bone Pain Trial Working Party (15, BPTWP). A hazard ratio of 1.5 implies that the hypofractionated radiation arm will have 35% of patients with treatment failure at 3 months. We expect to enroll 10 patients per month.

Randomization

Patients will be randomized to standard or hypofractionated radiation therapy using CORe. Randomization will be stratified by tumor size (≤ 4 cm vs. > 4 cm) , site of bony mets (extremities, pelvis, abdomen, head/neck, chest), and 1 vs >1 site irradiated. We expect approximately 40% of patients will have bony mets in the extremities and approximately 35% will have bony mets in the pelvis. We expect the distribution of patients enrolling will approximately be 40% lung malignancy, 25% genitourinary malignancy, 15% breast malignancy, 10% multiple myeloma and 10% other malignancy. We will have a total of 14 stratification levels.

Phase II

We will test the following hypothesis:

$$H_0: \rho = 1.5 \qquad \text{vs.} \qquad H_1: \rho = 1.0,$$

where ρ is the hazard ratio (hypofractionated/standard) for time to treatment failure, as defined in section 1.0. A sample size of 150 patients (75 randomized to each treatment arm) will yield 90% power with a 1-sided significance level of 0.20 to reject the null hypothesis (H_0) and conclude that hypofractionated treatment is not inferior to standard treatment in terms of time to treatment failure. We use a 1-sided significance level of 0.20 as recommended by Rubinstein et al. (16, Rubinstein) for phase II screening trials. This sample size will yield 110 events (i.e., treatment failures). It will take 15 months to enroll all the patients, and the maximum study duration is expected to be 22 months to observe the 110 events. The final analysis for phase II will be performed once

we've observed 110 events, and we will suspend accrual while we wait for these events to occur. We will continue to phase III only if we reject H_0 at the 0.20 significance level.

Phase III

We will test the following hypothesis:

$$H_0: \rho = 1.5 \qquad \text{vs.} \qquad H_1: \rho = 1.0,$$

where ρ is the hazard ratio (hypofractionated/standard) for time to treatment failure, as defined in section 1.0. We will need to observe 208 events to have 90% power to reject H_0 and conclude that the hypofractionated treatment is not inferior to standard treatment in terms of time to treatment failure with a 1-sided significance level of 0.05. The patients enrolled in the phase II part of the study will be included in the phase III part of the study. If we enroll 10 patients per month we expect to have to enroll 300 patients in total (150 randomized to each treatment arm) to observe these 208 events, requiring 30 months, or 15 months of additional accrual if we reject H_0 in the phase II part of the trial. We also expect to have to follow patients an additional 1 month after the last patient is enrolled before we observe the 208^{th} event. Thus, our trial duration is expected to be 22 + 15 + 1 = 38 months. If we haven't observed 208 events by month 38 we will conduct the final analysis once we've followed the last patient for 3 months. Our overall power is 90% × 90% = 81%, and our type I error rate in the phase III part of the study is 5%.

This sample size calculation was performed using East 5.4 (Copyright © 2010, Cytel Inc., Cambridge, MA).

Toxicity Monitoring

We will monitor the rate of radiation induced toxicity (skin dermatitis grade ≥ 4, gastrointestinal (GI) grade ≥ 3, genitourinary (GU) grade ≥ 3) by 12 months after the start of radiation therapy for the hypofractionated radiation therapy arm. We will enroll at least 25 patients and at most 150 patients on this treatment arm, and we will use the methods of Thall et al. (17, Thall et al.) to monitor the radiation induced toxicity rate. We will stop enrolling patients on the hypofractionated radiation therapy arm if we have reason to believe that the rate of radiation induced toxicity for this arm is more than 10%.

Formally, we will stop enrolling patients on the hypofractionated radiation therapy arm if Pr(radiation induced toxicity rate < 10% | data) < 0.10. That is, if there is less than a 10% chance that the rate of radiation induced toxicity is less than 10%, then we will stop enrolling patients on the hypofractionated radiation therapy arm.

We will actually monitor the time to radiation induced toxicity, because these toxicities may occur at any time from the start of radiation therapy. We will use the Clinical Trial

Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct) to monitor the toxicity stopping rule. This website is built and maintained by the Department of Biostatistics. The research staff will be trained by the study statistician in the use of the website to monitor the stopping rules, with an emphasis on the importance of updating toxicity outcomes and follow-up dates.

To obtain the operating characteristics for the stopping rule we simulated the trial 1000 times for various scenarios described in the table below. We assumed that patients are enrolled at the rate of 5 per month on the hypofractionated radiation therapy arm, that we would follow patients for 12 months, and that we will evaluate the stopping rule continually. The table below summarizes the operating characteristics of this stopping rule.

Operating Characteristics for the Toxicity Monitoring Rule

12-Month Toxicity Rate	Pr(Stop Early)	Sample Size			Avg Trial Duration (Months)
		P_{25}	Mean	P_{75}	
0.05	< 0.001	150	150	150	42.1
0.10	0.087	150	148	150	40.9
0.15	0.871	101	122	150	28.5
0.20	0.999	72	90	105	18.2

At any point in the trial time to radiation induced toxicity can be calculated for each patient, with the time interval regarded as censored at the date of last follow-up if toxicity has not been observed for a patient. We will apply a Bayesian method for updating prior information with time to toxicity data observed to that time. We assume that the time to toxicity for each patient is exponentially distributed with a median of λ_S months for the standard treatment and a median of λ_E for the experimental treatment. Given the historical data we assume λ_S follows an inverse gamma distribution with mean 78.95 months and a standard deviation of 0.15 months. The middle 95% of this distribution is between 78.66 and 79.24 months. These parameters correspond to a 12-month toxicity rate between 9.064% and 10.035%. We assume λ_E follows an inverse gamma distribution with a mean of 78.95 months and a standard deviation of 15.0 months. The middle 95% of this distribution is between 54.87 and 113.32 months. These parameters correspond to a 12-month toxicity rate between 7.077% and 14.066%.

Since the goal of the study is to achieve a toxicity rate of less than 10% at 12 months, the trial will be stopped early if, based on the available data, $Pr(\lambda_E < \lambda_S \mid \text{data from the trial}) < 0.10$. This rule was chosen to achieve an approximately 0.10 early stopping probability if the true toxicity rate is 10%.

Final Analysis

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients by treatment arm.

We will use the methods of Gooley et al. (18, Gooley) to estimate the cumulative incidence of treatment failure for each treatment arm with death as a competing event, and we will estimate the percent of patients without treatment failure at 3, 6, and 12 months for each treatment arm with a 95% confidence interval.

We will use the methods of Fine and Gray (19, Fine and Gray) to model time to treatment failure with death as a competing event and test the hypotheses stated above for phase II and for phase III. We will also estimate the hazard ratio for treatment with a 95% confidence interval.

We will use descriptive statistics and boxplots to summarize the score from the MDASI instrument at each assessment time. We will similarly summarize changes in scores for these instruments over time. We will use mixed effects regression methods with repeated measures and patient as a random effect to model instrument scores over time to test for treatment differences.

We will use the product limit estimator of Kaplan and Meier (20, Kaplan and Meier) to estimate overall survival and disease-free survival stratified by treatment arm. We will use Cox proportional hazards regression to model OS and DFS as a function of treatment arm, and we will estimate the hazard ratio for treatment with a 95% confidence interval (21, Cox).

We will use descriptive statistics to summarize narcotics use and acute and long-term adverse events for each treatment arm.

We will use Fisher's exact test to compare treatment arms with respect to the rates of re-irradiation and salvage surgery.

12. Database

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. [ref 22] REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2)

audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335.

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12. TABLE A: PATIENT ASSESSMENT CHECKLIST

Time	H&P	CBC	X-ray, CT, MRI, bone scan*	Path Dx	MDASI Survey	Phone call follow -up	Toxicity/AE assessment
Pre-RT	X	X	X	X	X		X
Within 7-10 days post XRT					X	X	
1 month post XRT[2]					X	X	
3 month f/u[1]			X		X		X
6 month f/u[1]			X		X		X
9 month f/u[1]			X		X		X
12 month f/u[1]			X		X		X
3-6 month interval thereafter (until death)			X		X		X

*Per standard of care

[1] **Within +/- 4 weeks**

[2] **Within +/- 1 week**

Time	H&P	CBC	X-ray, CT, MRI, bone scan*	Path Dx	MDASI Survey	Narcotic/ Opioid/ NSAID use	Toxicity/AE assessment
Pre-RT	X	X	X	X	X	X	X
Within 7-14 days post start of XRT by phone					X	X	X
1 month post start of XRT by phone[2]					X	X	X
3 month f/u[1]			X		X	X	X

6 month f/u[1]			X		X	X	X
9 month f/u[1]			X		X	X	X
12 month f/u[1]			X		X	X	X
3-6 month interval thereafter (until death)			X		X	X	X

*Per standard of care

[1] **Within +/- 4 weeks**

[2] **Within +/- 1 week**

13. APPENDIX A: NCI CTCAE version 4.03
14. APPENDIX B: The M.D. Anderson Symptom Inventory (MDASI) survey