PHASE I STUDY OF FRACTIONATED STEREOTACTIC RADIOSURGERY FOR LARGE BRAIN METASTASES

HCC # **11-091**

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1.0 Background:

Brain metastases are the most common intracranial tumor in adults, affecting up to 30% of all cancer patients (1-2). There are multiple treatment options for patients with brain metastases including surgical resection, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS) (3-8). Without treatment, the prognosis is poor, with survival limited to only a few months (9). Surgical resection is typically limited to patients with a good performance status, limited intracranial disease, patients with unknown primaries, isolated symptomatic lesions, and lesions that fail to respond to WBRT (10-11). Following resection, adjuvant WBRT is delivered with a typical course being 30 Gy in 10 fractions over 2 weeks. WBRT has been used for decades in patients with brain metastases and is thus very well-studied. The use of WBRT for patients with brain metastases from various primary cancers has been shown to improve existing neurologic symptoms and improve overall survival compared to corticosteroids and supportive care (median survival = 4-5 months) (12).

In more recent years, SRS has been shown to be an effective alternative therapy for patients with brain metastases. It is especially useful in patients with progression of disease following WBRT, for whom treatment-related neurotoxicity is a major concern. SRS allows for the delivery of a highly focused dose of radiation with rapid fall-off and thereby reduces dose to the surrounding normal brain. This feature should potentially reduce the likelihood of developing late neurocognitive deficits, an issue that becomes of increasing concern in long term survivors. SRS has been very well-studied in the setting of brain metastasis. In patients with brain metastases from a variety of primary cancers, SRS has shown to be both safe and efficacious with local control rates of 65-95% and an adverse radiation effect rate of 5-10% (13-15).

In the majority of SRS series, radiosurgery was delivered in a single fraction session. For patients with larger tumors it can be difficult to safely deliver an efficacious dose in a single SRS fraction. RTOG 90-05 (16) was a dose escalation study for patients with previously-irradiated brain tumors, 64% of which were brain metastases. In that study, patients with tumors with a diameter greater than 3 cm and treated to 18 Gy in a single fraction developed ≥ grade 3 toxicity at a rate of 50%. . The toxicities observed included irreversible edema, which necessitated steroids (15 of 156 patients), radionecrosis that necessitated surgical intervention (16 of 156 patients) or fatality (4 of 156 patients). It was determined that the maximum tolerable dose for these patients was 15 Gy. Tumor control was not reported according to size, but overall local control for all brain metastases was between 25-50% at 12 months, a figure much lower when compared to other SRS series. Therefore, a theoretical argument can be made for fractionation to spare normal tissues while delivering a biologically more effective dose. The advantages of fractionation include reoxygenation of the tumor cells, redistribution of tumor cells into more radiosensitive parts of the cell cycle, and a potential reduction in toxicity due to a lower dose per fraction (17-19).

Davey et al (20) published the outcomes of fractionated SRS for brain metastases in 69 patients. These patients were treated using a surgically attached head frame, meaning the first fraction was delivered at 6 pm on the first day followed by the second fraction at 8 am on the second day. All patients in this trial had tumors less than 3 cm in diameter. The prescription dose was 29.7 Gy prescribed to the 90% isodose line over 2 fractions. The outcomes in this cohort were compared to 35 patients that received 22.5 Gy in a single fraction. The median overall survival for patients treated with 2 fractions

was 30 weeks compared to 16 weeks in the single fraction group. In addition, patients treated with a single fraction were more likely to die due to their brain metastases (43% vs. 28%). Notwithstanding fractionation, other factors that predicted for improved survival were female gender, good performance status, solitary metastasis, and control of extra cranial disease. The authors did not report any toxicity in this paper, but 14 patients required operation for expanding masses, 13 of which were progressing disease and 1 that was radio necrosis.

We have recently reviewed the outcomes in patients treated with fractionated SRS at our institution (manuscript under review). We identified 45 patients with 47 metastases treated to a median dose of 20 Gy (range 13-27 Gy) in 2-3 fractions. With a median follow-up of six months there was an actuarial local control of 80% and 74% at 6 months and 12 months, respectively. These results are similar to the rates reported in single fraction SRS series. We would note, that on average, the tumors were larger in our series compared to others reported. It is also important to note that, compared to the patients treated in RTOG 90-05, our results were superior in terms of both local control (74% vs. 50%) and safety (0% grade3/4 toxicity vs. 15%). This data supports the use of fractionated SRS in the management of large brain metastases. With that in mind, we propose to determine a safe dose for fractionated SRS for large brain metastases, required for Phase II and III trials that will definitively characterize the efficacy of SRS in these patients.

2.0 Objectives

Primary Objective

2.1 To determine the maximum tolerated dose (MTD) and safety of fractionated SRS when treating brain metastases

- Primary Endpoint: Maximum Tolerated Dose: the maximum amount of Gy fractionated stereotactic radiosurgery (FSRS) delivered without significant toxicity

Secondary Objectives

2.2 To evaluate the local control associated with this therapy.

2.3 To evaluate regional intracranial failure associated with this therapy.

2.4 To evaluate the Health Related Quality of Life (HRQL) associated with this therapy.

Secondary Endpoints

- Local control: proportion of patients with Complete Response (CR), Partial Response (PR), or Stable Disease (SD) in the target lesion
- Regional intracranial failure: proportion of patients that develop new lesions outside the target volume
- Health Related Quality of Life (HRQL) measured by Functional Assessment of Cancer Therapy – General (FACT-Brain) assessment.

3.0 Investigational Plan

3.1 Overall design and plan of study

Prior to enrollment, all patients will be evaluated with a physical exam, review of pathology and laboratory values to confirm diagnosis, and baseline imaging studies

3.2 Accelerator

Physicians will treat patients with linear accelerator-based stereotactic radiosurgery system using 6MV photons.

3.3 Doses

Patients received a total dose of 24 to 36 Gy in 3 fractions (8-12 Gy/fx). Dose was escalated between patients as described in Section 7. The MTD has been determined to be 36 Gy at 3 fractions

In determining the radiation dose and fractionation scheme for this protocol, we used the linear-quadratic model for radiation cell killing to "equate" schemes that care the dose/fraction and number of fractions. This concept of biologically equivalent dose (BED) states that the total effect is given by:

$$n \times d \times (1 + d/(\alpha/\beta))$$

where n is the number of fractions and d is the dose/fraction. The "alpha-beta ratio" characterizes the radiation response of a particular tissue; a higher value is indicative of a tissue that responds acutely to the effects of radiation. Due to their highly proliferative nature, most tumors fall into this category.

This first dose scheme (total dose 24 Gy) is biologically equivalent to the previously studied best recommended doses in the literature (15 Gy, one fraction). We would favor treating in three fractions, as opposed to a single dose, to allow more repair of normal tissue, reoxygenation of tumor cells, and redistribution of tumor cells to more radiosensitive parts of the cell cycle. Using small fraction sizes, 8-12 Gy, will also help reduce late effects of radiation therapy. SRS treatment will be given on an every other day schedule, excluding weekends. The prescription dose will be prescribed to the isodose line best encompassing the planning target volume (PTV) depending on the volume of tumor

3.4 Localization, immobilization, and simulation

Patients will undergo CT simulation with intravenous contrast (contrast recommended, but not required). The patient will be set up in the CT scanner using a mesh mask for immobilization of the head while in the supine position. Additionally, an MRI with contrast, with Cyberknife sequences (i.e. ≤1.2mm slice thickness) is required, unless otherwise contraindicated (e.g. implanted ferromagnetic devices etc).

3.5 Treatment Planning

Treatment planning will be carried out using the appropriate radiosurgery treatment planning station. The gross tumor volume (GTV) will be contoured on the fused image set. A ≤2mm will be added for clinical target volume (CTV) or planning target volume (PTV). The treatment will be prescribed to the isodose line that best covers ≥95% the planning target volume, which will typically be the 80% isodose line.

3.6 Treatment Delivery

The planning data containing the coordinates of tumor isocenter, will be transferred to the appropriate platform depending on the treating machine. Treatments will be delivered over non-consecutive days, excluding weekends and holidays

3.7 Supportive Care

3.7.1 Prophylactic Anti-Edema Premedication: 1 hr prior to radiation (optional)

3.7.2 Decadron 4mg PO BID through the treatment course and for 1 week post-last SRS fraction

4.0 Patient Selection and Eligibility

4.1 Selection of Patients

Enrollment is defined as the first day of protocol therapy.

4.2 Number of Patients

A total of 25 patients will be enrolled.

4.3 Inclusion Criteria

All patients must meet the following criteria in order to be included in this study.

a. Male or female patients ≥ 18 years of age
b. A life expectancy of at least 12 weeks with a Karnofsky performance status of at least 70 (Appendix II)
c. The target lesion(s) can be accurately measured in at least one dimension according to RECIST
d. No prior radiotherapy to the brain
e. Previous or concurrent systemic or targeted chemotherapy is allowed
f. Patients must have an extra-cranial primary tumor diagnosis
g. Patients will have no more than 3 distinct lesions within the brain. At least 1 lesion must be a minimum of 3cm in greatest dimension, no larger than 5cm which will be treatable by fractionated stereotactic radiosurgery
h. The additional lesions will each be treated with single fraction stereotactic radiosurgery
i. Patient may be on steroids or anti-epileptics
j. Must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks and discomforts
k. Patients do not need a histologically proven diagnosis of brain mets

4.4 Exclusion Criteria

a. Symptomatic patients in need of surgery to the “target” lesion
b. Four or more newly-diagnosed lesions
c. Prior surgical resection of targeted tumor

d. Prior WBRT
e. Primary brain tumor
f. Pregnant or breast-feeding patients
g. Primary tumor histology of lymphoma, leukemia, multiple myeloma or germ cell tumor

5.0 TREATMENT EVALUATION, ADMINISTRATION, AND MODIFICATION

5.1.1 Tissue constraints

Treatment shall be delivered via linear accelerator (LINAC) commissioned and equipped to deliver stereotactic radiosurgery. Normal tissues and sensitive critical structures (e.g. spinal cord, brainstem, optic nerves, optic chiasm, and pituitary shall be contoured and the dose to these organs limited. Normal tissue constraints are outlined below.

Normal Tissue Constraints	
Organ	**Maximum Dose in 3 Fractions**
Spinal Cord	18 Gy
Brainstem	20 Gy
Optic Nerves	18 Gy
Optic Chiasm	18 Gy
Pituitary	20 Gy

5.1.2 Dose Specification, Homogeneity Considerations & Plan Evaluation

The treatment plan used shall be based on the assessment of the dose-volume histogram (DVH) with attention to coverage of the planning tumor volume (PTV) and critical normal structures.

The prescription dose is the isodose cloud that encompasses at least 80% of the PTV.

No more than 20% of any PTV shall receive doses >110% of its prescribed dose.

No more than 2% of any PTV shall receive <93% of its prescribed dose.

No more than 5% of any normal tissue shall receive doses in excess of 110% of the primary PTV dose.

5.2 On-Treatment and post-treatment toxicity evaluation

All patients will be seen prior to each fraction of stereotactic body radiotherapy and their toxicity evaluated by physical examination. Subsequently, patients will be evaluated for toxicity one month later and then every 8 – 12 weeks Toxicities will be scored by the NCI **CTCAE version 4.0**. Also see Section 6.0.

5.2.1 Stereotactic Radiosurgery Related-Toxicity

-SRS: Short-term side effects include but not limited to skin reaction, local hair loss, fatigue, nausea, vomiting, headaches, seizures, bleeding, or need for surgery. Long-term side effects are less likely to occur but if they do occur are more likely to be permanent. They include local hair loss, seizures, focal neurologic deficit, bleeding and symptomatic radiation necrosis.

5.2.2 CT-Related Toxicity

The subject will be exposed to radiation associated with the CT scans performed to complete treatment planning. CT scans are routinely performed as standard-of-care for tumor staging and to monitor response to therapy and the radiation dose associated with these diagnostic scans are felt to represent minimal risk. Patients will also receive MRI scans, which have no radiation and therefore no risk.

Claustrophobia: Possible anxiety, claustrophobia, and/or temporary discomfort may occur as a result of being placed in the scanning devices. Subjects will be monitored and removed from the scanner if required

5.2.3 Dose Levels for treatment

The dose levels are:

- 24 Gy in 3 fractions (8 Gy/fx) delivered on a minimum of every other day schedule for up to 2 weeks.
- 27 Gy in 3 fractions (9 Gy/fx) delivered on a minimum of every other day schedule for up to 2 weeks.
- 30 Gy in 3 fractions (10 Gy/fx) delivered on a minimum of every other day schedule for up to 2 weeks.
- 33 Gy in 3 fractions (11 Gy/fx) delivered on a minimum of every other day schedule for up to 2 weeks.
- 36 Gy in 3 fractions (12 Gy/fx) delivered on a minimum of every other day schedule for up to 2 weeks. This has been determined to be the MTD.

5.2.4 Definition of Dose Limiting Toxicities

Adverse Events will be graded for intensity according to the National Cancer Institute Common Toxicity Criteria, CTCAE Version 4.0. For the purposes of achieving the primary objective, which is determining the maximally tolerated dose of fractionated radiation, the dose limiting toxicity (DLT) will be defined as any adverse event that occurs within 60 days of treatment initiation of radiotherapy and meets any of the following criteria:

5.2.4.1
Grade 4 or worse or central nervous system necrosis, or cerebral edema, or encephalopathy, or intracranial hemorrhage, or myelitis, or seizure, or stroke, or,

5.2.4.2
Any toxicity causing radiation therapy to be withheld for more than two weeks that is not due to tumor progression, or,

5.2.4.3
Any other Grade 3 neurologic toxicity which does not improve to grade 2 within 60 days of treatment initiation of radiotherapy, or,

5.2.4.4
Any patient neurologic death within 60 days of treatment initiation of radiotherapy will be considered a DLT unless in the opinion of the study radiation oncologist and neurosurgeon, the death is definitely unrelated to treatment or death is definitely related to disease progression.

6.0 STUDY EVALUATIONS

6.1 Pretreatment Evaluation

The following tests/procedures will be performed in order to ascertain subject eligibility within 28 days prior to registration unless otherwise specified.

- Complete physical evaluation with a performance status, vital signs, height, and weight, and a complete medical history.
- Laboratory evaluation including complete blood counts with a platelet count and blood chemistry (approximately 3 teaspoons or 1 tablespoon).
- CT (computed tomography) Scan of the
- MRI (Magnetic Resonance Imaging) Scan of the brain
- For women of child bearing potential, a urine pregnancy test will be done. If this comes back positive or questionable, a serum pregnancy test will be completed by taking a small sample (about 1 teaspoonful) of blood. Pregnant women, or women who are currently breast-feeding an infant, will not be allowed to take part in this study.

In addition to the procedures listed above, the following Quality of Life questionnaire will be done for research purposes:

- FACT – BR (FACT – BRAIN) - This assessment will take approximately 5 (five) minutes to complete.

6.1.1 Treatment schedule

Parameter	Pre-Study	SRS			30 days post treatment	8-12 weeks post treatment	Q 8 – 10 weeks for 24 months post treatment
		Fx 1	Fx2	Fx3			
History	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X

Vital Signs	X				X	X	X
Measurement of disease by MRI	X					X	X
Performance Status	X				X	X	X
Hematologic Studies including CBC	X*						
CT Scan for treatment planning	X						
Serum or Urine Pregnancy Test for WOCBP	X						
FACT - Brain assessment	X				X	X	X
DLT Assessment					X	X	X

* Within 30 days of study start

6.2 Evaluation during treatment

The patient will be carefully followed while on active treatment and post-treatment for 24 months, or until death. Evaluation during treatment will consist of the following activities:

- Administration of stereotactic radiosurgery
- Interim medical history and physical examination at baseline and prior to each radiation therapy treatment.

6.2.1 Evaluations for Follow Up

- Patients will be seen in follow-up 30 days post treatment then at 8-12 weeks post-treatment and every 8-12 weeks for 24 months with the following evaluations:
- Complete physical evaluation with a performance status, vital signs, height, and weight, and a complete medical history
- Dose Limiting Toxicity Assessment
- MRI scans at 8-12 weeks post-treatment and every 8-12 weeks for 24 months for assessment of response to therapy and monitoring.
- Administration of Fact-Brain questionnaire 30 days post treatment, 8 -12 weeks post treatment, and at time of each follow-up visit/scan.

6.3 Study procedures

6.3.1 CT Imaging

A CT scan of the brain will be required. This scan will begin the preliminary mapping of the brain lesions. Secondly, a high resolution MRI will be performed to better plan necessary treatment.

6.4 Objective criteria for defining response

6.4.1. Tumor Response on MRI (RECIST)

Measurable Disease Response: CTEP's RECIST guidelines will be followed. A quick reference to the RECIST guidelines can be downloaded at the following URL: http://ctep.info.nih.gov/Policies/WordDocs/RCSTF.PH2TEMPF.doc. (Appendix II)

Patients enrolled in this study must have a measurable brain metastasis which is defined as lesions that can be accurately measured in at least one dimension: [longest diameter to be recorded] on the MRI scan.

The same method of assessment and the same technique should be used to characterize each identified & reported lesion at baseline & during follow-up.

Taking into account the measurement of the longest diameter only for those lesions with size response, response criteria are defined as:

1. Complete Response (CR): the disappearance of a target lesion. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
2. Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
3. Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as a reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. [21]

6.4.1.2 Definition of local control

In this study, patients will be recorded as having a lesion that is locally controlled if they have stable disease (SD), partial response (PR), or complete response (CR) in the target lesion; all of which are defined above. Patients will be recorded as having local failure if they have progressive disease (PD) within the target lesion. Patients that develop new lesions outside the target volume will be coded as having a regional intracranial failure. A distant failure will be defined as new brain metastases outside of the treatment volume.

6.4.1.3

HRQL studies (Fact-Brain) will be completed prior to treatment, and following treatment to coincide with follow-up exams and MRI scans. See appendix III for a full version of the Fact-Brain questionnaire.

7.0 Statistical Considerations

7.1 Definitions

Primary Objective

To determine the maximum tolerated dose (MTD) and safety of fractionated SRS when treating brain metastases

- Primary Endpoint: Maximum Tolerated Dose: the maximum amount of Gy fractionated stereotactic radiosurgery (FSRS) delivered without significant toxicity

Secondary Objectives

To evaluate the local control associated with this therapy.

To evaluate regional intracranial failure associated with this therapy.

To evaluate the Health Related Quality of Life (HRQL) associated with this therapy.

Secondary Endpoints

- Local control: proportion of patients with Complete Response (CR), Partial Response (PR), or Stable Disease (SD) in the target lesion
- Regional intracranial failure: proportion of patients that develop new lesions outside the target volume
- Health Related Quality of Life (HRQL) measured by Functional Assessment of Cancer Therapy – General (FACT-Brain) assessment.

The following definitions will be useful in explaining the trial design.

7.1.1 *Toxicity*

In this section, *toxicity* is taken to mean unacceptable, dose-limiting toxicity, as defined in Section 5.2.4, as any adverse event that occurs between the first fraction of radiotherapy and 60 days after the last fraction of radiotherapy. The primary goal of the TITE-CRM design employed in this trial is to identify the radiation dose associated with toxicity in 1/6=16.7% of patients (the MTD); this is referred to as the *target rate.*

7.1.3 *Expected rates of toxicity*

Based on previous treatment experience, the *expected rates of toxicity* have been estimated (Table 7.1). These rates will be re-evaluated throughout the trial as treatment experience is accrued in accordance with the TITE-CRM algorithm.

Radiation Dose	Expected Probability of Acute Toxicity
24 Gy	0.08
27 Gy	0.11
30 Gy	0.14
33 Gy	0.17
36 Gy	0.20

Table 7.1. Expected probabilities of toxicity

7.2 Escalation Rule

The trial will be monitored using a modification of the Continual Reassessment Method (24) called Time-to-Event CRM (25). The TITE-CRM method assumes a simple model for the time to occurrence of toxic response as a function of dose, and thereby allows information from all patients enrolled in the trial to be employed when allocating a new patient to a dose level. Subjects will be continuously recruited throughout the trial, without recruitment pauses between dose levels.

7.2.1 Initial dose

Dosing will begin at 24 Gy, which will cause toxicity in an estimated 8% of subjects.

7.2.2 Criterion for Dose Allocation

Doses will be allocated to patients according to the TITE-CRM algorithm:

a. Whenever a patient is presented for enrollment, the probability of toxicity will be estimated for each radiation dose, based on the initial expectations of toxicity (Table 7.1) and the incidence of toxicity in patients already treated, weighted by the amount of time those patients have been followed. The dose that has estimated toxicity closest but less than or equal to the target rate will be selected.

b. Dose escalation will be restricted to one level between adjacent patients. To be assigned to a dose greater than 24 Gy, at least one patient must have completed two months of observation post-treatment at the next lower dose without dose-limiting toxicity.

c. There is no restriction on the number of levels that the dose may be decreased between patients.

d. Under this allocation schema, the radiation dose will increase until toxicity is observed, and will then tend to vary around the dose associated with the target rate. In order to allocate doses, the protocol statistician must be notified promptly of all dose-limiting toxicities.

7.2.3 Dose-Toxicity Function

Given total dose d, a logistic dose-toxicity model with parameter α,

$$P(DLT|d)=e^{3+\alpha d}/(1+e^{3+\alpha d}),$$

Will be used, where α=1.0 represents the initial assumptions about the toxicity of treatment, as displayed in the 'Design' column of Table 7.1. This model, which has been widely used in CRM trials (24,26-29), is an approximation to the true, unknown, dose-toxicity model. The first two patients will be assigned to Level 1. When subsequent patients present for

enrollment, the expected probability of toxicity at each dose will be calculated, based on the prior distribution of α (Gaussian, with mean of 1 and standard deviation of 0.3) and the available data, using a SAS computer routine written especially for this application. The patient will be assigned to the level with estimated probability of toxicity closest to but not exceeding the target rate, 0.167, allowing for the escalation restrictions in Section 7.2.2.

7.2.4 Weighting of Enrolled Patients

In the TITE-CRM algorithm, patients are weighted in the calculation of the dose-toxicity function according to the proportion of the DLT observation period they have completed. Patients who have experienced DLT are assigned full weight (1), patients who have completed the eight-week post-treatment observation period without DLT are assigned full weight and patients still within the eight week post-treatment period, who have not experienced DLT are assigned a weight proportional to the fraction of the observation period they have completed. Because treatment will be completed within two weeks, the total observation period for the purposes of TITE-CRM will be assumed to be ten weeks from the day of the first fraction.

7.2.5 Operating characteristics

The operating characteristics of the trial design were evaluated in a simulation experiment. 750 TITE-CRM trials were simulated assuming the toxicity probabilities in Table 7.1, but with true toxicity probabilities as specified in Table 7.2. In simulations of Scenerio1, the assumed probabilities of toxicity are correct, but in Scenerio 2, the true probability is higher than assumed, and in Scenerio3 there is a jump in toxicity over the target rate between 27 Gy and 30 Gy.

Radiation Dose	Expected Probability of DLT	True Probabilities of DLT		
		Scenario 1	Scenario 2	Scenario 3
24 Gy	0.08	0.08	0.10	0.10
27 Gy	0.11	0.11	0.15	0.15
30 Gy	0.14	0.14	0.20	0.35
33 Gy	0.17	0.17	0.25	0.55
36 Gy	0.20	0.20	0.30	0.75

Table 7.2. Conditions for Monte Carlo Assessment of Operating Characteristics

The operating characteristics are described in Figure 7.1. Metrics described are numbers of patients treated at each dose, number of observed toxicity per dose, selected MTD and number of observed toxicity per trial. Roughly equal numbers of patients are treated at each dose in the first scenario (where the trial assumptions match the true probabilities of toxicity), with decreasing numbers of patients treated at higher doses in the second andthird scenarios. In the second and third scenarios, medians of 0 or 1 DLT per trial result from treatment at doses of 33 or 36 Gy. The chosen target dose tends to be somewhat conservative in all three scenarios. In the third scenario, in 56% of the trials result in either 24% or 28% of the patients on study experiencing DLT, due to the large jump

in toxicity across the true target dose, while, in the other scenarios, the proportions of patients on study experiencing DLT is less than or equal to the target rate of 1/6 in over 70% of the simulated trials. The proportions of treated patients experiencing DLT are similar to what would be expected from the 3+3 design, while the accuracy of the TITE-CRM design is actually slightly conservative compared to 3+3.

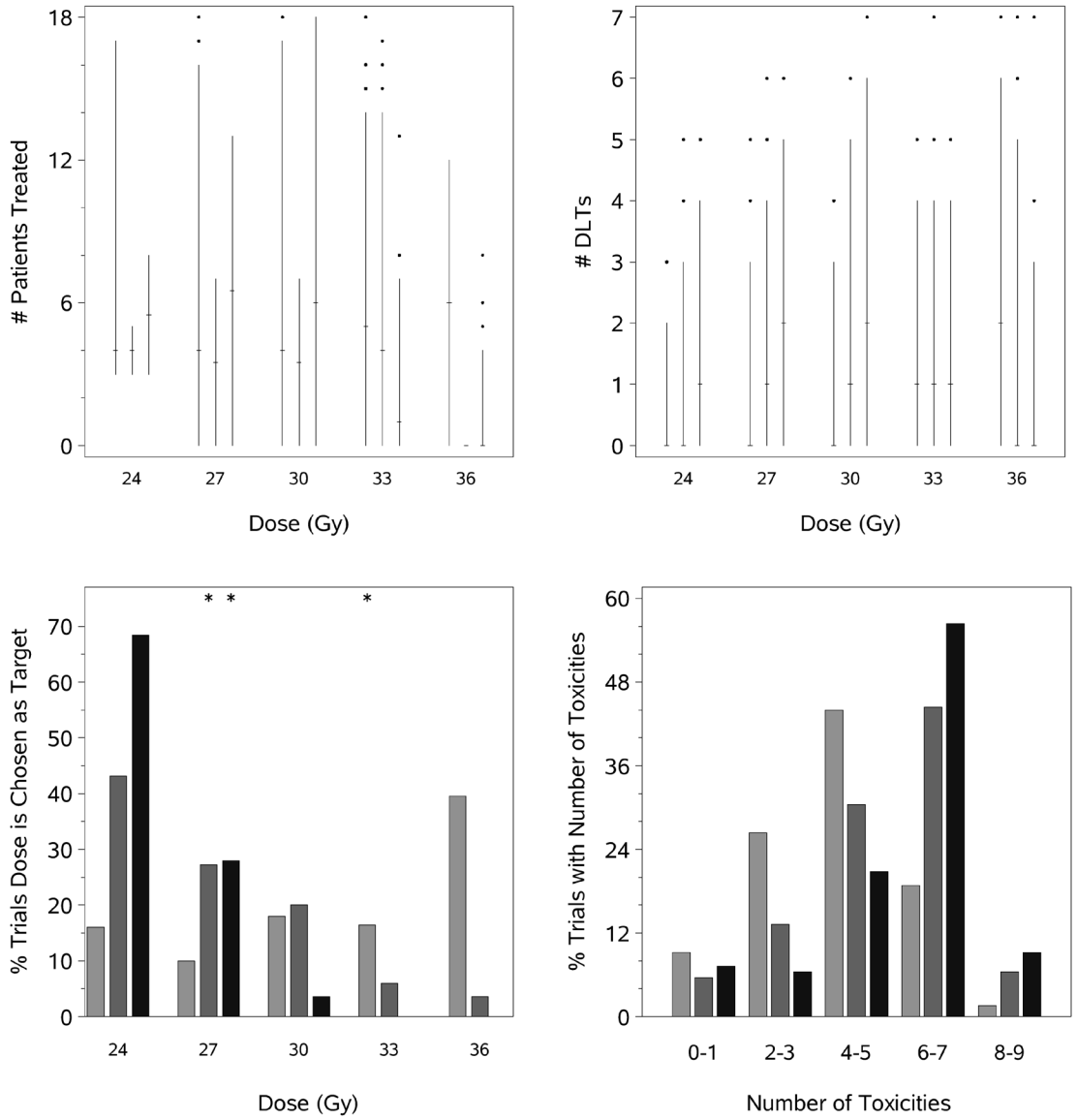

Figure 7.1 Operating characteristics of trial design. Bars from left to right in all frames indicate the first, second and third scenerios (Table 7.2). In the top frames, the tick marks indicate the medians, and the top and bottom of the bars the 97.5th and 2.5th percentiles, respectively. Asterisks in the bottom left frame indicate the true target doses for the three scenerios

7.4 Sample Size/Accrual Rate

No more than 25 evaluable patients will be treated in the trial. An evaluable patient is defined as one who either a) completes the three fractions and has no DLT until one month after the last fraction, or b) a patient who received at least one fraction and suffers DLT. Patients who are not evaluable will be replaced.

7.3 Data Analysis

When possible, generalized linear models (subsuming, for example, logistic regression) will be used to combine data from different dose levels. Model assumptions will be checked graphically prior to analysis. If model assumptions are not met, the analysis will be primarily descriptive. Baseline description statistics on all evaluable patients will be provided for demographic variables (age, sex, race/ethnicity), Karnofsky performance status, disease stage and status at the time of enrollment and treatment regimens previously used.

7.3.1 Analysis of the Primary Endpoint

1. Toxicities will be tabulated by category and grade. The proportion patients experiencing DLT at each dose will be calculated with 95% exact confidence intervals. The dose-toxicity function, describing the probability of DLT at each dose, will be estimated using logistic regression, along with likelihood ratio profile confidence intervals.

7.3.2 Analysis of Secondary Endpoints

2. The proportion patients experiencing local control at each dose will be calculated with 95% exact confidence intervals. The dose-response function, describing the probability of local control at each dose, will be estimated using logistic regression, along with likelihood ratio profile confidence intervals.

3. The probability of failure will be analyzed in a similar fashion to the probability of intracranial failure.

4. The analysis of HRQL data (Section 6.5.1.4) will be descriptive. The data will be summarized by question at each time point with the frequency and percentage of each quality level. For each patient, the trajectory of the score will be plotted against time.

8.0 Data Safety and Recording

8.1 Data and safety monitoring plan

All patient data will be collected by the Clinical Research Department of Radiation Oncology. All data will be secured in a password protected file with observance of all applicable HIPAA regulation. A data safety monitoring board will meet monthly to evaluate toxicity for this trial. Patients/adverse events will be discussed at the Radiation Oncology Data Safety meetings. Unexpected serious adverse events will be reported to the IRB and DSMC, and minutes of the monthly disease center meetings will be reviewed at the DSMC meetings. Reports will be submitted annually at the time of the yearly renewal.

8.1.1 Subject Removal Criteria

1. Disease progression
2. Development of a serious medical illness
3. Evidence of dose-limiting toxicity
4. Voluntary withdrawal
5. Severe Protocol Non Compliance
6. Discretion of the principal investigator
7. Development of grade 4 toxicity related to experimental therapeutic
8. Pregnancy

8.2 Safety Reporting

8.2.1 Acute Adverse Events

The CTCAE (described below) will be used to grade acute toxicity during this trial.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas will have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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

It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication.

Exacerbation of a pre-existing illness should be considered when a subject requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the study. Lack of or insufficient clinical response, benefit, efficacy, or therapeutic effect should not be recorded as an adverse event. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

In addition, abnormal objective test findings (e.g., electrocardiogram changes, abnormal laboratory test results) that can result in a change in study drug dosage or in discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the patient, should also be recorded as adverse events. Clinically significant changes in physical examination findings should also be recorded as adverse events. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the IRB or its designated representative.

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study drug will be recorded on the adverse event page(s) of the CRF. The investigator will record all adverse events in the CRF and assess each event as to severity and causal relationship to study drug.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

Attribution of the AE:
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

For all adverse events, sufficient information should be obtained by the investigator to determine the causality, (i.e., study drug or other illness). The investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse events that continue, or emerge within 30 days, after the patient's discontinuation or completion of the study will be followed until the events resolve, are considered stable, or can be ascribed to causes other than study treatment.

All serious AE shall be reported meeting criteria for reporting can be found on the University of Pittsburgh Institutional Review Board's website at http://www.irb.pitt.edu. In the event of such adverse event, the investigator must report the event(s) via phone within 24 hours and a written report filed within 24 hours to the Principal Investigator,.

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Appendix I

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

- **Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.**

Measurable disease **- the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- **All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).**
- **All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.**
- **All conclusions should be based on all eligible patients.**
- **Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.**
- **The 95% confidence intervals should be provided.**

Appendix II

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX III

Functional Assessment of Cancer Therapy – General (FACT-Brain)

Below is a list of statements that other people with your illness have said are important.

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

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

G P	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS	I am satisfied with my sex life	0	1	2	3	4

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

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4