A PHASE I/II STUDY OF INTRAOPERATIVE RADIOTHERAPY FOR PATIENTS WITH LARGE BRAIN METASTASES TREATED WITH NEUROSURGICAL RESECTION

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1.0 Schema

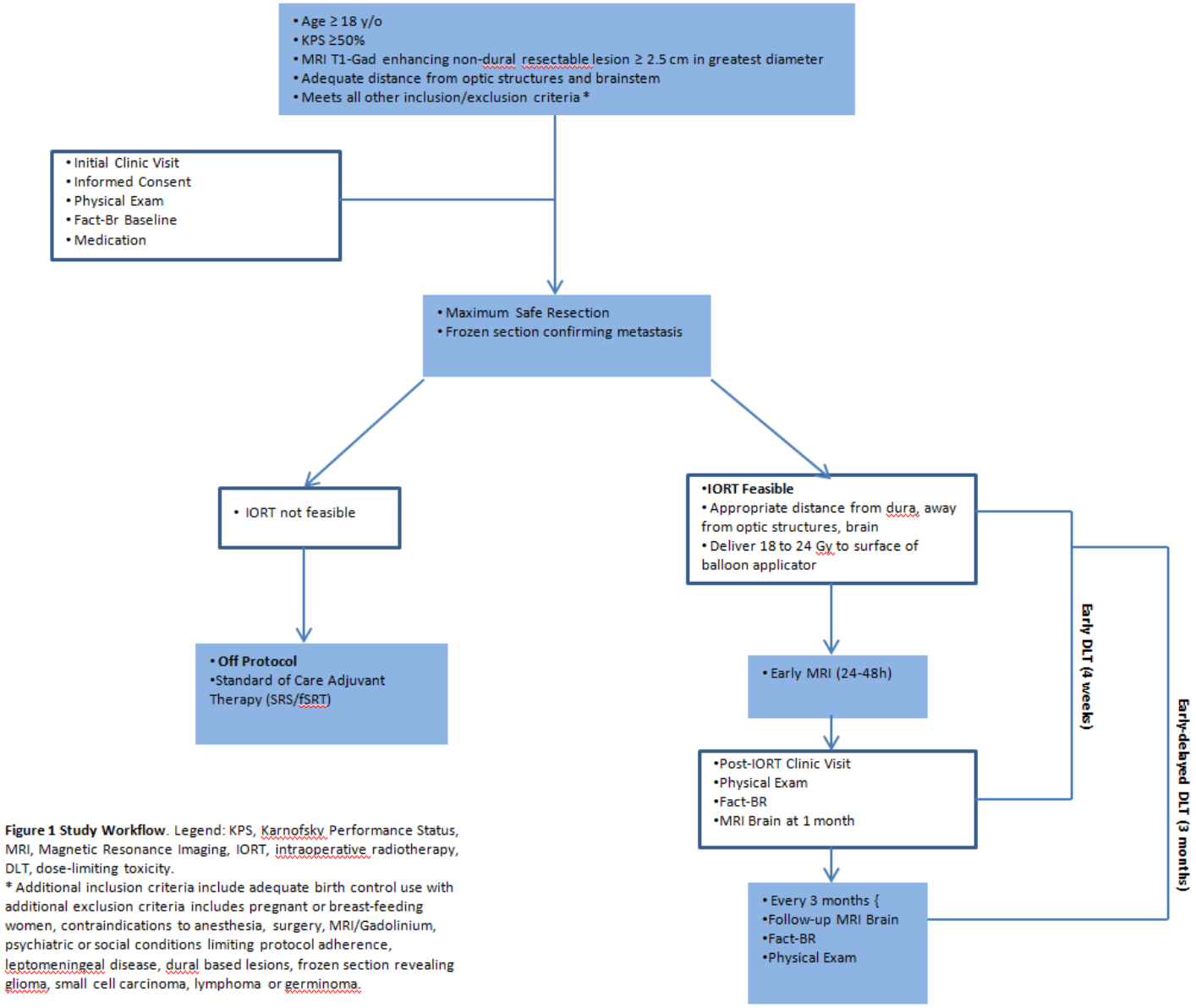

Figure 1 Study Workflow. Legend: KPS, Karnofsky Performance Status, MRI, Magnetic Resonance Imaging, IORT, intraoperative radiotherapy, DLT, dose-limiting toxicity.
* Additional inclusion criteria include adequate birth control use with additional exclusion criteria includes pregnant or breast-feeding women, contraindications to anesthesia, surgery, MRI/Gadolinium, psychiatric or social conditions limiting protocol adherence, leptomeningeal disease, dural based lesions, frozen section revealing glioma, small cell carcinoma, lymphoma or germinoma.

2.0 Objectives

1.1 Primary Objectives

1.1.1 To establish a maximum tolerated dose (MTD) through a dose-escalation trial using intraoperative radiotherapy (IORT) following neurosurgical resection for large brain metastases.

1.1.2 To determine median local progression-free survival, ie recurrence rate of treated brain metastasis

1.2 Secondary Objectives

1.2.1 Overall Survival

1.2.1.1 Differentiated between death secondary to systemic disease progression and neurologic death from intracerebral disease progression

1.2.2 Freedom from Further Treatment

1.2.2.1 Interval from IORT to further oncologic therapy (salvage radiosurgery, laser thermal therapy, etc)

1.2.3 Quality of Life (QOL)

1.2.3.1 FACT-Br

1.2.4 Global Progression Free Survival

1.2.4.1 Systemic Cancer Progression Free Survival

1.2.5 Intracranial Progression Free Survival

1.2.5.1 Time from IORT to development of new brain metastases

1.2.6 IORT Dose Limiting Toxicities

1.2.6.1 Craniotomy wound healing complications or infection requiring surgical intervention, intracranial hemorrhage, radionecrosis requiring intervention (surgical resection, laser intersitial therapy, prolonged (>7 days) steroid administration, avastin)

3.0 Background and Study Rationale

Brain metastases (BMs) are the most common intracranial tumor in adult patients and affect between between 10-30% of all patients with systemic malignancies [1]. It is estimated between 200,000 to 300,000 patients per year [2] are affected by brain metastases and the incidence of brain metastases will likely rise with the advent of increasingly effective systemic therapy. Therapeutic options for these patients commonly include definitive stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT) or surgical resection followed by adjuvant SRS or WBRT [3]. Given the improved prognosis for at least select groups of patients with novel systemic treatment, optimizing brain metastasis control while minimizing side effects of intracranial radiotherapy (RT) is increasingly critical.

Despite advances including more routine use of high precision SRS with submillimeter accuracy [4] and minimal dose to adjacent normal brain parenchyma, large brain tumors remain therapeutically challenging. Balancing the delivery of a sufficient dose of RT to achieve effective tumor control while minimizing treatment toxicity can be difficult to achieve for large tumors. When clinically appropriate, select brain metastases may be surgically resected with level I evidence demonstrating adjuvant SRS reduces local or tumor bed recurrence [5]. However, multiple prior investigations have suggested brain tumors with large preoperative diameter have worsened local control relative to smaller lesions even with postoperative SRS [6-8]. Further, patients may develop postoperative complications including wound healing which may delay adjuvant SRS and thus may increase the risk for tumor repopulation.

The potential for delivering ablative doses of radiation to the tumor bed while simultaneously sparing normal brain parenchyma from significant doses of radiation and reducing the potential for tumor repopulation has led to interest in the use of intraoperative radiotherapy (IORT). IORT has achieved excellent rates of local control in multiple prior series [9-13] and may be optimal for patients with large brain metastases. In contrast to postoperative radiosurgery, IORT does not require an interval for postoperative healing and cavity shrinkage, limiting potential tumor repopulation and conceivably disease spread beyond the surgical cavity [14]. Wernicke and colleagues recently published the results of a prospective protocol treating large (≥ 2.0cm) brain metastases undergoing surgical resection with IORT using a permanent Cesium-131 brachytherapy implant [9]. Their results were quite impressive, with a local/regional freedom from progression at 1 year of 80% for the subgroup of patients with tumors >3.0cm with a median follow up of 11.9 months. Further, they did not report any cases of radiation necrosis.

Delivering IORT for resected BMs using balloon based electronic brachytherapy with the Xoft Axxent device similarly facilitates single fraction treatment of the surgical cavity with a rapid dose falloff, exposing minimal normal brain parenchyma to doses of radiation [15]. Further, balloon based brachytherapy dose not require ordering a prespecified mesh impregnated with a radioisotope such as Cesium-131, eliminates the need for cutting mesh (potentially altering radioisotope placement), and removes the potential for post-implant radioisotope seed migration. Xoft electronic brachytherapy uses a disposable electronic radiation source producing 50 kV x-rays instead of a radioisotope (Cesium-131 has an energy rate of 30.4 keV). The electronic brachytherapy source may be turned on or off at will, and uses a similar technology to the photon radiosurgery system used in the intrabeam device [16]. The average treatment time ranges from 8 to 10 minutes.

An additional advantage of delivery electronic brachytherapy with kV energy is the minimal shielding requirement, with use approved for standard operating suites meeting the requirements for intraoperative fluoroscopy. The dose fall with Xoft is rapid, with the dose at 5mm and 10mm from the balloon applicator surface measuring 52.3% and 29.7% respectively for the small balloon applicator filled with 40cc of saline. Xoft IORT is commonly used when performing IORT for early stage breast carcinomas, with updated results

from an international, multi-institutional protocol treating more than 1200 patients from 2012 to 2018 presented at the 60th annual American Society for Radiation Oncology (ASTRO) meeting reporting excellent clinical outcomes (<1% in breast recurrence at 2 years) with minimal side effects.

In this protocol, we propose a phase I/phase II dose escalation study of large (≥ 2.5cm) brain metastases undergoing surgical resection treated with IORT using balloon applicator based electronic brachytherapy using the Xoft Axxent device. The starting dose will be 18 Gy prescribed to the surface of the balloon applicator, given the increased relative biologic effectiveness (RBE) of kV radiation (RBE ~1.3) this dose is considered ablative for residual microscopic disease with limited dose delivered to adjacent normal brain parenchyma well below documented tolerance thresholds. As the local control rate at 1 year for brain metastases with a preoperative diameter ≥ 3cm receiving postoperative SRS in the phase III trial by Mahajan et al was 58% [5], we believe the ability of IORT using the Xoft applicator to safely deliver a higher dose of RT to the tumor cavity may result in improved lesion control. The maximum dose tested will be 24 Gy prescribed to the applicator surface.

Dosimetric data investigating IORT plans using balloon applicator based electronic brachytherapy indicate IORT doses between 18 to 24 Gy produce plans with doses to organs at risk well below tolerance thresholds [12]. IORT doses within these dose levels have been demonstrated to be associated with acceptable toxicity in a phase I/phase II study using IORT followed by additional external beam RT to treated primary brain cancer (Glioblastoma) with no dose limiting toxicities occurring in their specified 3 month post IORT interval (doses from 20 to 40 Gy) [17].

4.0 Participant Selection

4.1 Inclusion Criteria

1. Participants must be ≥ 18 years of age.

2. Participants must have a Karnosfky performance status of ≥ 50%.

3. Participants must not have had prior intracranial radiation.

4. Participants must have a life expectancy greater than 3 months.

5. Participants must have a preoperative MRI Brain T1-Gadolinum enhanced scan demonstrating a non-dural based lesion with greatest diameter ≥ 2.5 cm.

6. Sufficient distance (≥ 2cm or at the discretion of the study principal investigator) of the intracranial lesion from optic structures (optic chiasm and bilateral optic nerves) and brainstem to meet established normal structure dose limits.

7. Subject or subject's legal representative to provide signed/written informed consent to participate in the study protocol.

8. Surface of balloon applicator must be ≥ 1cm from skin overlying closest portion of unresected calvarium.

9. Participants may remain on systemic therapy if they are receiving immunotherapy (anti-PD1, anti-PDL1, anti-CTLA-4), capecitabine, temozolomide, etoposide, vinorelbine, pemetrexed, lapatinib, traztuzumab, bevacizumab, mTor or ALK targeted agents with no break prior to initiating IORT.

9.1 Participants receiving cisplatin, methotrexate, taxanes, tyrosine kinase inhibitors, or BRAF targeted agents must have a seven day washout period prior to receiving IORT.

9.2 Participants receiving doxorubicin, T-DM1, or antibody-drug conjugates must have a fourteen day washout period prior to receiving IORT.

9.3. Participants receiving all other concurrent systemic agents will undergo consideration for a washout period prior to receiving IORT at the discretion of the study principal investigator.

4.2 Exclusion Criteria

1. Participants may not be pregnant or breast-feeding.

2. Patients must not have dural lesions or leptomeningeal disease.

3. Patients must not have psychiatric or social conditions limiting adherence to protocol guidelines.

4. Patients must not have contraindications to anesthesia, surgery, or MR imaging with Gadolinium injection.

5. Patients must not have a frozen section diagnosis of small cell carcinoma, lymphoma, germinoma or non-malignant histology.

6. Patients with additional unresected brain metastases must have a limited number of lesions/or volume of intracranial disease amenable to stereotactic radiotherapy at the discretion of the study principal investigator.

7. Patients deemed to require postoperative whole brain radiotherapy should be excluded.

4.3 Inclusion of Women and Minorities

1. Women and men including members of all races and ethnicity groups are eligible for this protocol.

5.0 Registration Procedures

5.1 General Guidelines

All eligible patients will be entered centrally into the Clinical Trials Management System at the University of Louisville by the designated study coordinator.

5.2 Registration Process

To register a patient, please ensure the completion of the following documents by the facility Research Nurse and fax or email the documents to the Study Coordinator:

- Copy of required pathology and imaging tests
- Signed patient consent form
- Other appropriate forms (e.g., Eligibility Screening Worksheet, Registration Form)

To complete the registration process the Coordinator will:

- Assign a unique patient protocol study number

- Register the patient on the protocol
- Create a study specific patient chart

The research nurse will ensure a copy of each patient's informed consent form is scanned in the patient's official medical record at the treating facility.

6.0 Treatment Plan

6.1 Surgical Resection

The resection procedure should be performed with image guidance (neuronavigation) with standard surgical technique. Resection techniques may include mono/bipolar cautery, suction or ultrasound aspiration. Maximal safe resection of tumor will be recommended. Ventricular opening intraoperatively should be avoided if at all possible to limit the potential for the accumulation of CSF/fluid around the balloon applicator, potentially modulating the delivered dose of radiation.

6.1.1 Frozen Section

Representative tissue samples must be sent intraoperatively for histopathologic examination/to establish the diagnosis of metastatic disease. Frozen section procedure will be performed in the standard fashion per facility protocol.

6.2 Intraoperative Radiation Therapy (IORT)

After the diagnosis of brain metastasis has been histopathologically established via confirmatory frozen section, preparations for IORT will be made. All potentially involved risk structures identified on preoperative imaging will be re-identified intraoperatively to ensure shifts after surgical resection resulting from changes in intracerebral pressure or CSF volume have not displaced the aforementioned structures with ultrasound or in-room CT/MRI. Constraints for the optic structures and brainstem with SRS detailed in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) of 12Gy (optic structures) and 12.5 Gy (brainstem) are commonly used [18] .

However, given the increased relative biological effectiveness of kV-irradiation[19] adapted dose contstraints of 10 Gy will be used for both the optic structures and the brainstem. Based on established dosimetric data [15,19] the dose delivered to tissue 1cm from the surface of the balloon applicator is between 6 to 7 Gy. Thus the aforementioned risk structures will receive well below threshold doses of RT using this criteria.

6.2.1 Applicator Size Selection

Optimal balloon applicator size will be selected with accordance to tumor bed/cavity geometry and adjacent normal brain parenchyma by the team of surgeons and radiation oncologists. A foley balloon catheter inserted into the tumor cavity and inflated with an appropriate volume of saline per cavity size may be utilized to help select optimal balloon applicator size. Applicator sizes range from 2.5cm to 3cm, 3 to 4cm and 4 to 5cm. The balloon applicator will be inserted into the cavity, and after insertion adjacent risk structures will again be evaluated using in room imaging (ultrasound or CT). It should be ensured any fluids surrounding the surface of the balloon applicator are removed.

6.2.2 Application of IORT

The radiation oncologist will place the miniature x-ray source inside the balloon shaped catheter placed inside the tumor cavity. Medical personnel may remain in the operating theater behind a rolling shield. Radiotherapy will be initiated by the treating radiation oncologist for a defined time interval calculated by the machine planning software.

After IORT has been delivered, the surgeon will remove the balloon applicator. Surgery will be continued in the regular fashion without additional requirements.

6.2.3 Radiation Safety

Federal and state safety regulations regarding radiation protection and the delivery of radiotherapy will be strictly adhered to with protocol delivery of IORT. Structural alterations of the operating suite will not be required as long as the operating room is approved for C-arm fluoroscopy [20].

7.0 Study Visits and Procedures

7.1.1 Visit 1: Screening/Enrollment

- Appropriately counsel patient on risks, rationale and benefits of protocol therapy
- Assess patient eligibility with regards to inclusion/exclusion criteria
- Obtain written informed consent from patient
- Obtain patient demographics and relevant medical history
- Perform a physical examination including height and weight
- Complete neurologic examination
- Assess preoperative Karnofsy Performance Status (KPS)
- Obtain vital signs including pulse, respirations, blood pressure and temperature
- Basic laboratory workup including CBC with differential, CMP
- Fact Br at baseline
- Pre-surgical MRI of the brain performed within 28 days of planned resection
- Subject enrollment notification form must be submitted immediately upon study consent
- Completed case report form must be submitted within 7-14 days after each visit

7.1.2 Visit 2: Short Interval Post-Operative Visit (within 4 weeks of IORT)

- Interim medical history
- Complete Neurologic and Physical Examination
- KPS evaluation
- FACT-BR completed by patient or representative
- Review of early postoperative MRI (≤72 hours of resection) with removal of ≥98% of the T1 Gadolinium enhancing lesion deemed a complete resection, and less 98% deemed a subtotal resection
- Medication review
- Completed Case Report Form must be submitted within 7-14 days after each visit

7.1.3 Visit 3: (3 months after IORT completion)

- Interim medical history
- Complete Neurologic and Physical Examination
- KPS evaluation
- FACT-BR completed by patient or representative.
- MRI of the Brain (with and without Gadolinium contrast)
- Adverse event reporting
- Survival/Documentation of Local/Distant brain metastasis recurrence
- Completed case report form must be submitted within 7-14 days after each visit

7.1.4 Visit 4 (6 months after IORT completion)

- Interim medical history
- Complete Neurologic and Physical Examination
- KPS evaluation
- FACT-BR completed by patient or representative.
- MRI of the Brain (with and without Gadolinium contrast)
- Adverse event reporting
- Survival/Documentation of Local/Distant brain metastasis recurrence
- Completed case report form must be submitted within 7-14 days after each visit

7.1.5 Visit 5 (9 months after IORT completion)

- Interim medical history
- Complete Neurologic and Physical Examination
- KPS evaluation
- FACT-BR completed by patient or representative.
- MRI of the Brain (with and without Gadolinium contrast)
- Adverse event reporting
- Survival/Documentation of Local/Distant brain metastasis recurrence
- Completed case report form must be submitted within 7-14 days after each visit

7.1.6 Visit 6 (12 months after IORT completion)

- Interim medical history
- Complete Neurologic and Physical Examination
- KPS evaluation
- FACT-BR completed by patient or representative.
- MRI of the Brain (with and without Gadolinium contrast)
- Adverse event reporting
- Survival/Documentation of Local/Distant brain metastasis recurrence
- Completed case report form must be submitted within 7-14 days after each visit

7.2 General Concomitant Medication and Supportive Care Guidelines

Anti-emetic, steroid or anti-epileptic medications may all be used at the discretion of the treating physician.

7.3 Duration of Follow up

Survival status will be collected every 3 months up to 1 year from IORT completion, then every 6 months until death. Local recurrence (nodular enhancement within the tumor bed), and distant intracranial progression (development of brain metastases outside of the resection cavity) will be monitored during the same intervals. Documentation for survival status should include both the date and cause of death.

7.4 Criteria for Removal from the Study

Participants will be removed from the study when any of the criteria listed in section 8.2 applies. The specific reason for study withdrawal and the date of removal will be documented in the study-specific case report form. Alternative therapeutic/care options will be discussed with the participant.

In the event of a severe or life-threatening adverse event, the participating investigators must immediately alert the principal investigator.

8.0 Expected Toxicities and Dose Modifications

Dose limiting toxicities will be assessed on the basis of clinical presentation with assessment of physical exam, KPS assessment, baseline medications, MRI Brain (preoperative imaging compared to subsequent scans including early postop), neurologic examination, and adverse event grading using the CTCAE v5.0.

8.1 Early (≤4 weeks of IORT) Dose Limiting Toxicities

- Wound healing complications or wound infection requiring surgical intervention
- Cerebral hemorrhage or ischemia attributable to IORT
- Transient worsening of existing neurological deficits limiting ADLs (activities of daily living)
- New or Recurrent Seizures Refractory to Antiepileptic Regimen
- Severe Headaches (CTCAE v 5.0 grade 3)

8.2 Early-Delayed DLTs (≤ 3 months after IORT)

- Symptomatic radiation necrosis requiring surgical intervention, laser thermal therapy or bevacizumab
- Transient worsening of existing neurological deficits limiting ADLs
- New or Recurrent Seizures Refractory to Antiepileptic Regimen Seizures
- Severe Headaches (CTCAE v 5.0 grade 3)

9.0 Study Calendar

Visits	Pre-Study	V1	V2	V3	V4	V5	V6
		Screening	Early Postop				
			≤ 4 weeks after IORT	3 months after IORT	6 months after IORT	9 months after IORT	12 months after IORT
MRI/Tumor Assessment	X (≤28 days before resection)		X (≤ 72 hours after IORT)	X	X	X	X
Inclusion/Exclusion		X					
Informed Consent		X					
Demographics		X					
Medical History		X					
Interim Medical History			X	X	X	X	X
Physical Exam		X	X	X	X	X	X
Neurologic Exam		X	X	X	X	X	X
KPS		X	X	X	X	X	X
Vitals		X	X	X	X	X	X
FACT-BR		X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X
Adverse Event Reporting			X	X	X	X	X
Survival/Disease Progression			X	X	X	X	X
Case Report Forms		X	X	X	X	X	X

10.0 Measurement of Effect

All subjects will have standard magnetic resonance imaging (MRI) of the brain (with and without Gadolinium contrast) within 4 weeks (28 days) of surgical resection to assess preoperative tumor size and within 72 hours of resection/IORT to assess for residual tumor. Subsequent MRI Brain scans will be ordered every 3 months for the 1st year to determine tumor bed control/distant control (freedom from brain metastasis development outside resection cavity). After 1 year, MRI brain scans will be ordered every 6 months until death. All postoperative/IORT scans will be reviewed to assess for recurrent disease in the tumor bed, new brain metastases, infection or radiation necrosis.

MRI is the standard imaging modality used in this protocol. All MRI scans will be recommended to include axial, coronal and sagittal sequences performed with and without gadolinium contrast enhancement.

10.1 Response Criteria

10.1.1 Local Control

Recurrence in the tumor bed will be defined as the development of new nodular or contrast enhancement within 5mm of the resection cavity on T1-gadolinium contrasted MRI of the Brain.

10.1.2 Freedom From Further Therapy

Freedom from further therapy will be defined as the interval from IORT completion to additional treatment targeting the initial resection cavity including stereotactic radiosurgery, laser interstitial thermal therapy, or additional surgical resection.

10.1.3 Distant Brain Control

Distant brain failure will be defined as the development of brain metastases on T1-gadolinium contrasted MRI of the Brain elsewhere in the brain parenchyma (>5mm from the tumor cavity).

10.1.4 Radiation Necrosis

Radiation necrosis will be determined radiographically using contrast enhanced MRI of the Brain with consideration of additional MRI sequences including perfusion and diffusion imaging. Cases of questionable radiation necrosis versus local failure in the tumor bed will be discussed at our institutional multidisciplinary Central Nervous System tumor board with consideration of advanced MRI sequences including MR Spectroscopy in accordance with national Neuro-Oncology recommendations [21].

10.1.5 Overall Survival

Overall survival will be defined as the interval from protocol enrollment to death from any cause. Surviving patients at time of analysis will be censored at time of last follow up.

10.1.6 Neurologic Death

Neurologic death will be defined as patients dying with progressive neurologic decline regardless of extracranial disease status. Patients deemed to die of intercurrent disease with severe neurologic function will also be considered to have had neurologic death. This definition is consistent with prior investigations [22,23].

11.0 Additional Response Parameters

Quality of Life will be assessed for this protocol using the FACT-BR (brain) validated questionnaire [24]. FACT-BR measures general quality of life, reflecting symptoms or problems associated with brain malignancies across 5 scales. These scales detail information regarding physical well-being, social/family well-being, emotional well-being, functional well-being, and disease specific concerns. The questionnaire is written at 4th

grade reading level and can be filled out in less than 10 minutes. No pre-certification is required for the self-reported quality of life and can be completed by the patient or with assistance of the examiner.

All pertinent and required permissions for use of the FACT-BR instrument have been obtained.

12.0 Data Safety Monitoring Board

Progress for this protocol will be monitored and reviewed by the Brown Cancer center Data Safety Monitoring Board (DSMB). Summaries of the protocol data will be provided by the Biostatistics Office after review by the Principal Investigator (PI). Data will include information regarding patient accrual, summary of demographic information, CTCAE grade 3 or 4 toxicities, and major adverse events including death or recurrent disease.

13.0 Study Design/Statistical Analysis

13.1 Sample Size

This study will be conducted in 2 phases.

Phase I:

We will use the classical 3+3 dose-escallation design during the phase I portion. We anticipate requiring to enroll between 12-18 patients in phase I pending DLTs. We will allow at most 5 grade 3-4 DLTs in phase I in order to proceed to phase II. If any deaths attributable to protocol therapy are observed or ≥ 6 grade 3-4 DLTs, we will halt the trial.

The Brown Cancer Center Data and Safety monitoring plan will be used for this phase I/II protocol. Continuous review of data including patient safety will be peformed by the study investigators. Quarterly summaries of severe adverse events (SAEs) will be submitted through the Clinical Trials Office to the DSMB.

Phase II:

Twelve month local control of large (≥ 3cm) resected brain metastases receiving single fraction postoperative radiosurgery was 58% in the recently published phase III trial by Mahajan and colleagues. A recently published phase II protocol of patients with large resected brain metastases treated with intraoperative RT using cesium brachytherapy meshes demonstrated a 12 month local control of 80%. We assume $p_0 = 0.60$ (12 month local control is at most 60% if protocol therapy is not effective) and $p_1 = 0.80$ (12 month local control is anticipated to be 80% or higher). Using Simon's two-stage Minimax design with $\alpha = 0.05$, $\beta = 0.20$ (power =80%), a maximum of 35 patients will need to be enrolled. Thirteen patients will need to be enrolled for initial stage, and an additional 21 will be enrolled in the second stage. Table S1 provides further detail regarding sample size justification. Please note patients from phase I at the MTD will be included in initial stage of phase II for protocol efficacy estimation.

Table S1. Sample Size Justification with $P_0=0.60$, $P_1= 0.80$, $\alpha = 0.05$, $\beta = 0.20$

Two-stage Design	MiniMax Design
First Stage Sample Size (n1)	13
Upper Limit for 1st Stage Rejection (r1)	8

Maximum Sample Size (n)	35
Upper Limit for 2nd Stage Rejection (r)	25
Expected Sample Size if Response Probability = P_0	21
Probability of Early Termination at P_0	0.65

13.2 Study Design

This is a phase I/II study of patients with large (≥2.5cm in greatest preoperative diameter) resected brain metastases treated with intraoperative radiotherapy using the Xoft electronic brachytherapy system.

Phase I will be a dose-escalation study performed in a classical 3+3 manner, with 3 patients entering at each dose level. Initially, 3 patients will be treated with IORT using the Xoft system to a dose of 18 Gy prescribed to the surface of the Xoft balloon applicator. The decision to escalate to the next dose level (21 Gy prescribed to balloon applicator surface) will be based on safety assessment after all 3 patients treated at the prior dose level (18 Gy) have reached 3 months (90 days) from completion of IORT.

If no dose-limiting toxicities (as previously described) occur in the initial cohort of 3 patients after 90 days of follow up after IORT completion, the next three patients will be treated at the next dose level (21 Gy prescribed to applicator surface). If 1 of the 3 patients in the initial cohort of 3 patients experience a DLT, an additional cohort of 3 patients will be treated at the same dose level. If no DLTs occur in the additional cohort, dose escalation will proceed to the subsequent dose level. If ≥ 1 patient in the additional cohort experiences a DLT, the maximal tolerated dose (MTD) is considered exceeded and dose escalation will stop.

If ≥ 2 patients at a dose level experience a DLT, the MTD will be considered to have been exceeded and the MTD will be defined as the preceding dose level. If only a total of 3 patients were tested at the potential MTD (preceding dose level), this potential MTD will be confirmed by recruiting an additional cohort of 3 patients to be tested at the potential MTD. If ≤1 patients experience a DLT, the MTD will be confirmed. If ≥ 2 patients experience a DLT, the preceding lower dose level will be considered as the potential MTD.

If no DLT occurs, the highest dose level (24 Gy prescribed to applicator surface) will be considered the MTD.

Phase II will then initiate. The first stage will require enrolling 13 patients (patients from phase I receiving MTD of IORT will be included for efficacy estimation). Phase II will terminate if 5 or more of these 13 patients experience local failure, and Phase II will proceed if 8 or more maintain 12mo local control. After this determination, an additional 22 patients will be enrolled.

13.3 End-Point Definitions

13.3.1 Primary Endpoint: The primary endpoint for phase I will be toxicity of therapy. Toxicity will be measured using the National Cancer Institute Common terminology criteria for adverse events (version 5.0). Rates of symptomatic brain radionecrosis (requiring medical interventions including surgical resection) are very low in recent reported series of patients with resected brain metastasis (<5%) [9,12].

13.3.2 Secondary Endpoints: Secondary endpoints of interest will include local control, freedom from further therapy, distant brain control all measured from time of enrollment to event. Quality of life will be assessed using the FACT-BR questionnaire at each of the aforementioned time points (study calendar).

13.4 Statistical Analysis

Patients receiving protocol treatment will be included in the presented analyses. Patients who received protocol treatment who are later discovered to have not fully met the protocol eligibility criteria will be presented. Patients who do not complete required observations will be listed, detailed and evaluated separately as necessary. All reasons for study withdrawal and date of withdrawal will be presented.

Descriptive statistics using the chi-square, Kruskal-Wallis and Fisher exact tests will be to characterize baseline patient demographic, treatment and tumor related factors for the study cohort. Kaplan-Meier methods and the log-rank test will be used to estimate survival outcomes including overall survival, local control and distant control. Multivariable Cox regression will be used to evaluate prognostic factors associated with survival.

Descriptive statistics will also be used to characterize toxicity incidence rates in the study cohort. Multivariable logistic regression will be performed to identify factors associated with grade 3 or 4 adverse toxicity.

The relationship between quality of life using the FACT-BR instrument and demographic, tumor and treatment related factors will be explored using a mixed linear regression model [25]. Each of quality of life scales examined in the FACT-BR instrument will be examined using a set of mixed linear regression analyses using the 6 study time points (calendar) as within-patient factors, and assuming an autogressive correlation structure of the first order. This model will ensure repeated measures in the same patient are not evaluated as independent observations, and ensures patients with some missing data are not excluded entirely from the analysis but contribute results at the study time points where values are available. This will ensure patients who died before protocol completion are included for quality of life analysis until death.

All analyses will be performed using the R project for statistical computing software, version 3.3.1[26]

13.5. Monitoring Rule for Phase I/II

Monitoring of the accumulated outcomes data will be designed to ensure the continuing safety of the currently enrolled participants and participants not yet enrolled. To ensure the above, this protocol may be stopped prior to accrual to reduce the number of participants exposed to a suboptimal treatment.

13.6 Non-efficacious Treatment (Futility):

In the first stage if phase II, 13 patients will be enrolled. If 8 or fewer patients fail to demonstrate local control of the treated tumor bed at 12 months, we will not enroll any further patients. If 9 or more patients demonstrated local control at 12 months, we plan to enroll a further 22 patients. In order for the protocol therapy to be declared effective, at least 26 patients must have local control of the tumor bed at 12 months. If the 12 month local control is 60%, we have a 65% chance of stopping the protocol early, and at the most, 21 patients will have received potentially ineffective therapy.

Statistical References:

1. Dean CB, Nielsen JD: Generalized linear mixed models: a review and some extensions. Lifetime Data Anal 13:497-512, 2007

14.0 Adverse Events

14.1 Definition of an Adverse Event

Adverse Events (AEs) are defined as worsening of an existing medical condition in a protocol participant administered an investigational (medicinal) product or new development of an untoward medical occurrence. A causal relationship between the adverse event and the investigational product is not necessary. Any unfavorable/unintended sign (abnormal laboratory value), symptom or disease associated with the investigational product, whether considered related to the product or not can be considered an AE.

Adverse events should be spontaneously reported, or elicited during an open-ended line of questioning, evaluation or examination of the protocol participant. Direct questioning regarding the specific occurrence of one or more AEs should be avoided to minimize reporting bias.

Adverse events will be recorded continuously from signing of informed consent.

Adverse events will be graded using the National Cancer Institute Criteria for Adverse Events (CTCAE) Version 4.0. (Appendix 17.3)

14.2 Definition of a Serious Adverse Event

An adverse event, whether considered to be associated with the treatment protocol or not, will be classified as a Serious Adverse Event (SAE) in accordance US Food and Drug Administration regulations (FDA) when it meets any of the following criteria:

- Result in Death
- Is life threatening (patient is at immediate risk of death)
- Requires inpatient hospital admission or prolongs existing hospital admission (please note: planned hospital admission or outpatient surgery due to an existing condition will not be regarded as a SAE in this study)
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Or other important medical events that based on appropriate medical judgment are believed to jeopardize the patient and/or require medical or surgical intervention to prevent one of the other outcomes defining an SAE

Any SAE ongoing when the patient ends study participation, regardless of relationship to protocol treatment, will be followed with appropriate therapeutic management and documented in the study records until the SAE resolves or is stabilized.

14.3 Required Action for Serious Adverse Events

All SAEs related or unrelated to protocol treatment must be reported to the Coordinating Center, the James Graham Brown Cancer Center (JGBCC) within 24 hours of knowledge of the event. All SAEs occurring after consent will be reported via the Clinical Trial Serious Adverse Event Form.

Supporting medical documentation for SAEs must be submitted as soon as available to supplement missing information (this may include but is not limited to hospital admission records, discharge summaries, autopsy reports, etc.).

Follow up SAE reports must be submitted as soon as the relevant information is available to supplement any missing information.

Final reports must be submitted upon resolution or stabilization of the SAE.

Investigators are responsible for reporting all serious and/or unexpected adverse events to the reviewing IRB/EC per local regulations. The original report must be maintained at the investigative location and filed in the regulatory file. A copy of the completed report must be submitted to the JGBCC.

15.0 Administrative

15.1 Case Report Forms

The principal investigator (PI) will be supplied with Case Report Forms (CRFs) associated with the study protocol. CRFs should be completed by the PI or delegated personnel. Information entered onto the CRFs must be verified by source documents. Completed CRFs and supporting source documentation must be submitted to the JGBCC within 7 to 14 days after completion of each study visit.

15.2 Source Documents

Information documented on CRFs should be verifiable using source documents. Records considered source documents include but are not limited to hospital records, clinical charts, radiologic data, lab and pathology reports.

15.3 Protocol Deviations

The PI is responsible for documenting and reporting all protocol deviations to the coordinating center, as soon as possible (but no more than 5 business days from knowledge), and for complying with IRB procedures for reporting deviations.

16.0 References

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17.0 Appendices

17.1 Performance Scoring Criteria

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severly disabled. Hospitalisation indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

17.2 Toxicity Criteria (CTCAE v5.0)

For naming and grading of adverse events, please use the NCI CTCAE v5.0 which may be referenced using the following hyperlink:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

17.3 FACT-BR (Version 4)

FACT-BR (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during 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
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the 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
GE6	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

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An 10	I get headaches	0	1	2	3	4