Northwell Lenox Hill Hospital

PID # 23-004 IMPROVING OUTCOMES IN PATIENTS WITH METASTATIC CANCER TO THE BRAIN WITH PRE-OPERATIVE FRACTIONATED RADIOSURGERY (fSRS): A PILOT STUDY

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Improving Outcomes in Patients with Metastatic Cancer to the Brain with Pre-Operative Fractionated Radiosurgery (fSRS): A Pilot Study
Study Description:	This study addresses a critical unmet clinical need by prospectively investigating preoperative fractionated stereotactic radiosurgery (fSRS) for large brain metastases. This approach offers a promising strategy to mitigate concerns regarding local recurrence within the resection cavity, leptomeningeal disease (LMD), and radiation necrosis (RN), which are frequently observed with current postoperative SRS. Hypothesis: We hypothesize that preoperative fSRS will lower failure rates by enabling more accurate target delineation and a smaller treatment volume, thereby reducing RN-associated toxicity. Furthermore, treating the disease before surgical manipulation may decrease LMD rates, potentially mitigating brain-related complications and preserving neurocognition.
Objectives:	**Primary Objective:** To determine the local progression-free survival (PFS) within the resection cavity in patients with brain metastases treated with preoperative fractionated stereotactic radiosurgery (fSRS). **Secondary Objectives:** To **assess** the incidence of leptomeningeal disease (LMD), radiation necrosis (RN), and neurocognitive function in patients receiving preoperative fSRS. **Exploratory Objectives:** To correlate pathologic information from the primary cancer and resected brain metastasis, along with the extent of surgical resection, with progression-free survival (PFS) and overall survival (OS).
Endpoints:	**Primary Endpoint:** • Local freedom from progression (FFP) within the resection cavity for patients treated with preoperative fractionated stereotactic radiosurgery (fSRS). **Secondary Endpoints:** • Rates of leptomeningeal disease (LMD). • Rates of radiation necrosis (RN). • Neurocognitive function outcomes *(All secondary endpoints will be assessed in patients treated with preoperative fSRS)* **Exploratory Endpoints:** • Comparison of pathologic information between the primary cancer and resected brain metastasis

	Correlation of the extent of surgical resection with progression-free survival (PFS) and overall survival (OS)
Study Population:	The proposed sample size for this study is 12 evaluable subjects. We define evaluable subjects as those who meet all eligibility criteria, are enrolled in the study, and complete preoperative fractionated stereotactic radiosurgery (fSRS). The proposed sample size for this study is 12 evaluable subjects defined as subjects that meet all eligibility criteria, were enrolled into the study and completed pre-operative fractionated stereotactic radiosurgery (fSRS).
Criteria for Inclusion and Exclusion:	**Inclusion Criteria** To be eligible for this study, all the following conditions must be met: • Age: Patient is ≥18 years old. • Brain Metastases: Radiographic confirmation of 1-5 brain metastases by MRI with contrast obtained within 4 weeks prior to registration. One of these must be an index lesion requiring surgical resection. • Index Lesion Size: The maximum diameter of the index lesion, as measured on any orthogonal plane (axial, sagittal, coronal) on the post-contrast MRI, must be ≥2.0 cm and ≤5.0 cm. • Cancer Diagnosis: Documented pathological diagnosis of active or history of invasive cancer within the past 5 years. • Lesion Location: All brain metastases must be located ≥5 mm from the optic chiasm and outside the brainstem. • Medical & Surgical Feasibility: Patient can medically tolerate surgery and fSRS. The treating surgeon must deem the index lesion an appropriate target for safe resection. • Performance Status: Karnofsky Performance Status (KPS) ≥50 within 14 days prior to registration. • Pregnancy Test: A negative urine or serum pregnancy test (for individuals of childbearing potential) ≤14 days prior to registration. • Informed Consent: Patient or legally authorized representative provides study-specific informed consent before study entry. For patients treated in the U.S., authorization permitting release of personal health information is also required.

	Exclusion Criteria Patients will be excluded from this study if any of the following conditions are met: • Prior Cranial Radiotherapy to the Resection Site: Previous cranial radiotherapy, including whole-brain radiotherapy or stereotactic radiosurgery (SRS), to the planned resection site (index lesion). Repeat radiosurgery to the same location/lesion is not permitted on this protocol. *Note: Prior or current fSRS/SRS to other non-index lesions is allowed.* • Leptomeningeal Disease (LMD): Evidence of leptomeningeal disease. • Inability to Undergo MRI with Contrast: Any contraindication or inability to undergo MRI with contrast. • Concurrent Systemic Therapy: Planned administration of cytotoxic chemotherapy or tyrosine/multi-kinase inhibitors within 3 days prior to, on the day of, or within 3 days after the completion of fSRS. *Note: Chemotherapy and immunotherapy administered outside of this specific window are permitted.*
Phase	Pilot Study
Description of Sites/Facilities Enrolling Participants:	Lenox Hill Hospital Manhattan Eye, Ear, and Throat Hospital (MEETH)
Description of Study Intervention:	This study will assess the outcomes of preoperative fractionated stereotactic radiosurgery (fSRS) for brain metastases undergoing neurosurgical resection. We will assess the local control (LC) and incidence of leptomeningeal disease (LMD) and radiation necrosis (RN) using this preoperative approach..
Study Duration:	2 years

1.2 SCHEMA

Flow diagram: N/A

2 INTRODUCTION

2.1 STUDY RATIONALE

There is a significant unmet clinical need for a prospective study in patients with brain metastases≥ 2cm using pre-operative fSRS as potentially effective therapy to address concerns of LC, LMD, and RN that are currently seen after post-operative SRS.

2.2 BACKGROUND

Metastasis from primary cancer commonly involves the brain, with an incidence of 5-14% (1). Triple negative breast cancer (TNBC) and Her-2 positive/receptor negative BC are among the most common breast cancer types that result in brain metastasis (BM) (2). The reported incidence of BM from these types is 14-38% (3,4), compared to 10% or less in the luminal subtype (4). The prognosis of patients with BM from various histologic subtypes also varies; Darlix et al showed a median OS 18.9 months for HER2+/HR+ , 13.1 months for HER2+/HR-, 4.4 months for triple-negative and 7.1 months for HER2-/HR+ patients ($p < 0.0001$) (5) Niikura et al. reported a median survival of 9.3 months in luminal subtype, 16.5 months luminal-HER2 type, 11.5 months for HER2 type, and 4.9 months for TNBC (6). Brain metastases are also common in the setting of metastatic lung cancer, colon cancer, to name a few. Brain metastasis prognostic models include the RPA (recursive partitioning analysis) (7), the diagnosis-specific Graded Prognostic Assessment (GPA) prognostic model, and a modified breast-GPA model (8,9). Treatment options for BM from BC usually follow BM from other primary sites such as lung cancer, melanoma etc. NCCN (National Comprehensive Cancer Network) describes the current treatment recommendations (10).

Post-operative Radiation for Brain metastasis: Surgical resection for BM is offered to patients who require pathological confirmation, have a large (≥ 2 cm) metastasis, or are acutely experiencing mass effect or neurological symptoms refractory to steroids (10). Post-operative stereotactic radiosurgery (SRS) diminishes the risk of local recurrence in smaller lesions, but metastases larger than 4cc (diameter ≥ 2cm) still recur at 37% within 1 year and have an inferior survival (11). Additionally, the rate of leptomeningeal disease (LMD), in the post-operative SRS is 30%, especially in patients with breast cancer histology (11). Adding whole brain radiation therapy (WBRT) reduces increases local recurrence (12,13). Given concerns of neurocognitive decline after WBRT, the paradigm has shifted to postoperative SRS (14-16). Figure 1 shows a representative case treated with post-operative SRS and developed LMD shortly thereafter and succumbed to death within 2.5 months.

Rationale for pre-operative fSRS: Pre-operative radiation therapy (RT) may improve outcomes by improving LC and decreasing adverse effects. Lower rates RN will be expected since the pre-operative SRS margins and volumes are smaller than the ones with post-operative SRS. In fact, the literature reports that post-resection planning target volume (PTV) margins

(which account of the uncertainty of surgical manipulation) for post-operative SRS increases the post-operative volume by ~28% (17). Also, pre-operative RT may reduce the risk of tumor spillage and subsequent LMD which is often seen in post-operative SRS, and this is especially true for brain metastasis from breast cancer primary (18). In addition, up to 30% of patients do not receive their prescribed course of post-operative RT due to treatment non-compliance, medical/surgical complications, or delays in referral (19-20). Therefore, planned pre-operative SRS may improve compliance and completion of prescribed RT regimen. Fractionation (giving 3 gentler treatments amounting to a higher overall dose rather than a single large dose), may facilitate safer delivery of higher biological effective dose (BED) treatments, which may improve the high local failure rates as seen in studies mentioned above.

Pre-operative versus post-operative and 'fractionated' (fSRS) versus 'single fraction' stereotactic radiosurgery (SRS): Single fraction SRS does have a significant local recurrence rate. In the pre-operative SRS outcomes and prognostic factors from a large multicenter cohort (Preoperative Radiosurgery for Brain Metastases [PROPS-BM]) study (21), patients with BM from solid cancers who had at least 1 lesion treated with preoperative SRS and underwent a planned resection were included from 5 institutions. There were 242 patients/253 index lesions. The single fraction median dose was 15 Gray. Cavity local recurrence (LR) rates at 1 and 2 years were 15% and 17.9%, respectively. Subtotal resection was a strong independent predictor of local recurrence. In the Brown study, comparing single fraction SRS to whole brain radiation therapy (WBRT) post-operatively, 6-month surgical bed control was 80.4% in the SRS group versus 87.1% in the WBRT group (p=0·00068) (22).

In a study by Mahajan et al (23), patients had a complete resection of 1-3 brain metastases (maximum diameter of the resection cavity ≤4 cm). Patients were randomly assigned (1:1) to either SRS of the resection cavity or observation. The median postoperative RT dose was 16 Gy (range 12–18). LR in the treated site was 24% in the SRS group versus 48% in the observation group. In a retrospective, multi-institutional analysis (24) of pre-operative fSRS for large or symptomatic BM, 53 patients with 55 lesions were eligible for analysis. The median gross tumor volume (GTV) volume was 12 cc and the median PTV volume was 19 cc. The median radiation dose was 24 Gy (range of 24–25 Gy). All patients either received 24 Gy in 3 fractions or 25 Gy in 5 fractions. The median time from last radiation fraction to surgery was 2 days and the 12-month survival probability was 70%. Twelve percent experienced radiographic RN of any grade, 1 patient experienced grade 2 RN, 2 patients experienced grade 3 RN. There were 0% LFs, and 1 LMD occurrence. In a retrospective analysis (25) comparing pre-operative fSRS to postoperative SRS/fSRS, 279 patients with surgical resection for BM were analyzed. The median follow-up (FU) time was 9 months. The median PTV for pre-operative and post-operative treatment was 14 cc and 38 cc, respectively ($p < 0.001$). The median RT dose was 24 Gy (range of 14–30 Gy) on linear accelerator, and 18–20 Gy with Gamma Knife (all Gamma Knife treatments were single fraction). For preoperative fSRS, the median time from last RT to surgery was 2 days. The rates of LF, grade 2 or higher RN, and LMD with postoperative fSRS (n = 189) were 4.2 %, 9 %, and 5.3 %, respectively, for a composite endpoint incidence of 17 % versus 0 %, 5.7 %, and 1.9 % with preoperative fSRT (n=53), respectively, for a composite endpoint incidence of 7.5 %. The authors concluded that preoperative fSRS is well-tolerated

with an objectively low rate of LF, LMD, and RN and without a delay in time to surgery or elevated rate of surgical complications (25). The authors concluded that there is a need for prospective evaluation.

To date, prospective evidence for pre-operative SRS is limited. A phase I dose escalation trial published as an abstract (26) examined outcomes in 27 patients treated with pre-operative SRS. The LF at 1 year was 28 %- and 1-year LMD rate was 4% and RN was not documented (26). In a study (27) that included a mixture of prospective and database patients (n=47), pre-operative SRS was delivered with a median of 1 day prior to surgery. Local control (LC) was 97.8%, 85.6%, and 71.8% at 6, 12, and 24 months respectively. OS (Overall Survival) was 60% at 12 months. LF was more likely with lesions >10 cc (p=.01), >3.4 cm (p=.014), with a trend in surface lesions (p=.066) and eloquent areas (p=.052). An additional mixed prospective plus retrospective experience (28), the efficacy and toxicity of preoperative SRS was evaluated. Surgery followed within 48 hours (about 2 days). 117 patients with 125 lesions were treated with single-fraction preoperative SRS and planned resection. Of the 117 patients, 24 patients were enrolled in an initial prospective trial and the remaining 93 cases were consecutively treated patients who were retrospectively reviewed. LR at 2 years was 25.1%, distant brain failure, 60.2%; LMD, 4.3%; and symptomatic RN, 4.8%. The median OS and 2-year OS rate were 17.2 months and 36.7%, respectively. Subtotal resection predicted cavity LR and worsened OS in multivariable analyses (28). An ongoing study is comparing pre-operative SRS versus post-operative SRS (29). Table 1 summarizes the LC, LF, LMD rates, RN rates, OS between preoperative versus postoperative RT treatments.

Table 1.

Historical data	Pre-operative SRS	Post-operative SRS/fSRS	Pre-operative fSRS
Local recurrence	25% at 2 y (28) 28% at 1y (24) 29% at 2y (27) 17% at 2 y (21)	4.2% (fSRS) (25) 20% (SRS) (22) 24% (SRS) (23)	0% (25) 0% (24)
LMD	4.3% at 2 y (28) 4% at 1y (26)	5.3% fSRS (25)	1.9%
RN		9% fSRS(25)	5.7%
Survival	17 months (median) 60% at 1y (OS)	12.2 months median OS (22)	Unknown

Our proposal addresses the significant unmet clinical need for a prospective study with pre-operative treatments of fSRS to large brain metastases as a potentially effective therapy to address concerns of local (resection cavity) recurrence, LMD, and RN that are currently seen with post-operative SRS.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Side effects include but not limited to Radiation Necrosis, Brain Injury, Seizures, skin toxicity, Nausea/Vomiting, infection, complications from hospital admission from radiation toxicity, cognitive and neurological complications, nerve, and bone damage.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits include longer survival compared to historical treatments, reduced side effects compared to historical treatments, better quality of life compared to standard of care, better cancer control compared to standard treatments.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Risks will be assessed using the CTCAE v 5.0 toxicity. Cancer outcomes such as disease-free survival, and overall survival will be documented.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this study is to determine local (resection cavity) freedom from progression (FFP) in patients with metastatic cancer to the brain treated with pre-fSRS.	To assess this objective, we will enroll 12 patients with metastatic cancer to the brain size >2cm as determined by the pre-fSRS MRI who will be treated to 27Gy in 3 fractions with fSRS 1 week (+/-5 days) prior to surgical resection. These patients will be followed with post-operative MRI 48-72 hours (considered a baseline MRI for purposes of disease assessment) and MRIs every 3 months for 2 years. Local FFP is defined as the absence of new nodular contrast enhancement of 2 mm or less from the resection cavity.	Local control (LC) or FFP is an objective measure of response on the MRI studies
Secondary		
The secondary objectives are to assess rates of LMD, RN, and neuro-cognitive function in patients treated with pre-fSRS.	To assess this objective, we will use the same MRI schedule, as mentioned in primary objective, to assess incidence of LMD and RN on imaging. Further, we will test neuro-cognitive function as measured by the Montreal Cognitive Assessment (MoCA).	
Tertiary/Exploratory		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To compare pathologic information of resected brain metastasis, extent of surgical resection and correlate with PFS and OS.		

4 STUDY DESIGN

4.1 OVERALL DESIGN

This prospective single arm trial includes 3 Specific Aims.

In **Specific Aim 1, we will determine local (resection cavity) freedom from progression (FFP)** in patients with metastatic cancer to the brain treated with pre-fSRS. To assess this aim, we will enroll 12 patients with a metastatic cancer to the brain size ≥2cm as determined by the pre-fSRS MRI who will be treated to 27Gy in 3 fractions with fSRS 1 week (+/-5 days) prior to surgical resection. These patients will be followed with post-operative MRI 48-72 hours (considered a baseline MRI for purposes of disease assessment) and MRIs every 3 months for 2 years. Local FFP is defined as the absence of new nodular contrast enhancement 2 mm or less from the resection cavity.

In **Specific Aim 2, we will assess rates of LMD, RN, and neuro-cognitive function in patients treated with pre-fSRS.** To assess this aim, we will use the same MRI schedule, as mentioned in Specific Aim 1, to evaulate the incidence of LMD and RN on imaging. Further, we will test neuro-cognitive function as measured by the Montreal Cognitive Assessment (MoCA).

In **Specific Aim 3, we will perform the following exploratory objectives: compare pathologic information from primary cancer to the one of the resected brain metastasis, extent of surgical resection and correlate with PFS and OS. Montreal Cognitive Assessment:** The MoCA is a 10-minute cognitive test validated in >50 languages (including English, French, and Spanish). 30 items are contained in the MoCA: short-term memory (5 points); visuospatial abilities via clock drawing (3 points), and a cube copy task (1 point); executive functioning via an adaptation of Trail Making Test Part B (1 point), phonemic fluency (1 point), and verbal abstraction (2 points); attention, concentration, and working memory via target detection (1 point); serial subtraction (3 points), digits forward (1 point), and digits backward (1 point); language via confrontation naming with low familiarity animals (3 points), and repetition of complex sequences (2 points); and orientation to time and place (6 points) (30).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

As discussed in section 2.2 (Background), We hypothesize that pre-operative fSRS has the potential to decrease the rate of local failure by using more accurate target delineation with a smaller target volume, thereby decreasing RN as associated toxicity. In addition, if the rates of LMD are reduced by treating the disease prior to surgical manipulation of the metastatic tumor, the risk of brain death can be reduced, thus positively impacting neurocognition.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or last scheduled procedure shown in the Schedule of Activities (SoA), Section 8.1.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

Patients age >18 years of age, with a biopsy or prior pathologic diagnosis of cancer and metastatic disease to the brain, with one of the brain metastases requiring surgery.

Subjects will be the patients of the investigator and being seen for an initial consultation as per standard of care. Subjects will be recruited in the Department of Radiation Medicine through three different means: Daily Smart Rounds, Screening through the electronic medical system (EMR) and Tumor Boards. Investigators can identify their own patients as prospective subjects. Additionally, the research team will proactively screen the investigator's patient schedule to seek out potential subjects for the study. Prescreening for study eligibility will be conducted by authorized Northwell Health personnel, including the Principal Investigator, Clinical Research Coordinators, Clinical Research Nurses, and Nurse Navigators. These individuals are Northwell Health workforce members with role-based access to patient schedules and the EMR and will perform prescreening in accordance with applicable Northwell Health privacy, confidentiality, and HIPAA requirements. Together, across all the Radiation Network sites, there should be enough subjects to achieve the study goal.

5.1 INCLUSION CRITERIA

A patient cannot be considered eligible for this study unless ALL the following conditions are met:

1. Age $\geq$18 plus Radiographic confirmation of 1-5 brain metastases, one of which requires resection (index lesion), as defined by MRI with contrast obtained within 4 weeks prior to registration.

2. The maximum diameter of the lesion to be radiated on the post-contrast MRI, as measured on any orthogonal plane (axial, sagittal, coronal), must measure ≥ 2.0 cm and ≤ 5.0 cm.

3. Known active or history of invasive primary cancer based on documented pathologic diagnosis within the past 5 years.

4. All brain metastases must be located ≥ 5 mm from the optic chiasm and outside the brainstem.

5. Patients can medically tolerate surgery and fSRS. The lesion chosen (index) for surgical therapy must be deemed an appropriate target for safe resection by the treating surgeon.

6. Karnofsky Performance Status (KPS) ≥ 50 within 14 days prior to registration.

7. A negative urine or serum pregnancy test (in persons of childbearing potential) ≤ 14 days prior to registration.

8. The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

5.2 EXCLUSION CRITERIA

1. Prior cranial radiotherapy, including whole brain radiotherapy, or SRS to the resection site. Note: The index lesion to be resected cannot have been previously treated with radiation (i.e., repeat radiosurgery to the same location/lesion is not allowed on this protocol).

Note: Previous or current fSRS/SRS to other lesions is allowed.

2. Evidence of leptomeningeal disease (LMD).

3. Inability to undergo MRI with contrast.

4. Planned administration of cytotoxic chemotherapy or tyrosine/multi-kinase inhibitors within the 3 days prior to, the day of, or within 3 days after the completion of fSRS.

Note: Chemotherapy and immunotherapy outside of this window are allowed.

5.3 SCREEN FAILURES

Screen failures are defined as patients who have provided informed consent and who fail to satisfy all criteria for participation in this trial. Due to the timepoints of the study, subjects will only be rescreened if the study is amending the eligibility criteria. Medical care of these patients will continue unchanged in all other respects.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be accrued in the Department of Radiation Oncology as well as Department of Neurosurgery preferably after tumor board discussion. Eligible patients will be presented with an option to enroll in the study. Any decision about each patient's enrollment will need approval of the radiation oncologist as well as the treating neurosurgeon.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Research Plan: Patients will be accrued in the Department of Radiation Oncology after a multidisciplinary tumor board discussion. Patient radiation plans will be prepared in such a manner so that all radiation treatments will be completed within 1 week (+/- 5 days) prior to surgery. Preoperative fSRS to a dose of 27Gy in 3 fractions will be delivered to the index lesion that is identified to be resected and will be treated every other day. The lesion subject to resection will be the index lesion and the resulting cavity after resection will be monitored for local recurrence. If there are additional lesions (5 or less), all lesions will be treated with SRS (<2cm) or fSRS (≥2cm) based on departmental guidelines. However, only the index lesion will undergo resection after pre-op fSRS. **Local recurrence (LR)** will be defined as recurrence within 2 mm of resection cavity. Recurrence in another radiated (but not resected) lesion will be defined as **distant recurrence.** New lesions recurring in another part of brain that was neither resected nor radiated will be called **new distant metastases**.

Radiation Planning: This protocol requires photon treatment. Proper immobilization/patient localization is critical and mandatory for this protocol and achieved using appropriate clinical devices. A noninvasive thermoplastic mask-based immobilization will be performed.

Simulation: Contiguous CT slices of 1.25 mm slice thickness or less will be obtained. CT scan should cover from top of head to bottom of skull. Contrast enhancement during CT-simulation is permitted. MR imaging is required for the study and shall be used for target delineation. Image fusions must be performed by a qualified medical physicist and reviewed by the attending physician.

Contouring: The GTV (Gross target volume) is defined as the enhancing metastasis on a gadolinium enhanced MRI scan. CTV (Clinical target volume) is defined as identical to GTV. The PTV (planning target volume) is defined as identical to CTV or as the CTV plus an optional symmetrical 1.0 mm margin. Organs at risk (OAR) dose constraints will be as per TG 101 publication.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a single arm prospective study. No randomization will be done.

6.3 STUDY INTERVENTION COMPLIANCE

Patient compliance will be monitored and documented by the investigator and delegated research personnel. Patients will be provided clear, detailed instructions on the intervention during the informed consent process. In addition, patients will be provided a copy of the informed consent to refer to for detailed instructions regarding the intervention. Intervention is pre-operative fSRS. The fSRS procedure is standard, the timing of preop fSRS is intervention.

Research personnel will provide a protocol calendar to each patient to ensure the patient fully understands the protocol procedures and timelines. Investigator and research personnel will closely monitor each patient's time of surgery to ensure it meets the required time frame of within 1 week (+/- 5 days) post-SRS, per protocol.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, and supplements.

Patients will be receiving radiation prior to surgery. After surgery, systemic treatment can be considered as per the institutional standards.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from systemic treatment or not opting for systemic treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive surgery.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and receive

the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may also be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they miss a scheduled visit and the study team is unable to reach them after three contact attempts, including one certified letter sent to the patients last known address after two unsuccessful contact attempts.

If a participant misses a study visit:

- Within 1 business day of the missed visit, the site will try to contact them to reschedule.
- Before categorizing them as lost to follow-up, the investigator or their designee will make every effort to reach them. This includes at least two phone calls. If two attempts to contact the participant are unsuccessful, a certified letter will be sent to the patient's last known address asking them to contact the study team.

If the study team still can't reach the participant, they will be withdrawn from the study due to being lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCHEDULE OF ASSESSMENTS

Assessment	Within 4 Weeks Prior to Registration (+/- 1 Week)	Prior to Pre-Op fSRS * (+/- 1 Week)	Post-Op Visits (Timing)	Follow-Up (Every 3 Months+/- 2 Weeks for 2 Years)
History & Physical Exam, including Weight	X	X		
Medical History	---------- X ----------			
Karnofsky Performance Status & Neurologic Function	X			X
Surgical Consultation	X			
MRI Brain with Contrast	X		X[1]	X
Neurocognitive Function (MOCA)	X		X	X
Serum or Urine Pregnancy Test[3]	X	X		
Adverse Events			X[2]	X

Pathologic Confirmation of Brain Metastasis			X	

[1] within 24-72 hours of surgery
[2] within two weeks of surgery
[3] Pregnancy test to be done ≤14 days prior to registration.
* Radiation treatments will be completed within 1 week (+/- 5 days) prior to surgery

8.1.1 EFFICACY ASSESSMENTS

Patients will be accrued in the Department of Radiation Oncology after a multidisciplinary tumor board discussion. Patient radiation plans will be prepared in such a manner so that all radiation treatments will be completed within 1 week (+/- 5 days) prior to surgery. Preoperative fSRS to a dose of 27Gy in 3 fractions will be delivered to the index lesion that is identified to be resected and will be treated every other day. The lesion subject to resection will be the index lesion and the resulting cavity after resection will be monitored for local recurrence. If there are additional lesions (5 or less), all lesions will be treated with SRS (<2cm) or fSRS (≥2cm) based on departmental guidelines. However, only the index lesion will undergo resection after pre-op fSRS. **Local recurrence (LR)** will be defined as recurrence within 2 mm of resection cavity. Recurrence in another radiated (but not resected) lesion will be defined as **distant recurrence.** New lesions recurring in another part of brain that was neither resected nor radiated will be called **new distant metastases**.

Radiation Planning: This protocol requires photon treatment. Proper immobilization/patient localization is critical and mandatory for this protocol and achieved using appropriate clinical devices. A noninvasive thermoplastic mask-based immobilization will be performed.

Simulation: Contiguous CT slices of 1.25 mm slice thickness or less will be obtained. CT scan should cover from top of head to bottom of skull. Contrast enhancement during CT-simulation is permitted. MR imaging is required for the study and shall be used for target delineation. Image fusions must be performed by a qualified medical physicist and reviewed by the attending physician.

Contouring: The GTV (Gross target volume) is defined as the enhancing metastasis on a gadolinium enhanced MRI scan. CTV (Clinical target volume) is defined as identical to GTV. The PTV (planning target volume) is defined as identical to CTV or as the CTV plus an optional symmetrical 1.0 mm margin. Organs at risk (OAR) dose constraints will be as per TG 101 publication.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product or therapy and which does not

necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product or investigational procedure, whether it is related to the protocol specified procedure or investigational product.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered an SAE if, in the view of either the investigator, or sponsor it:

1. Is life-threatening **or**
2. Results in in-patient hospitalization or prolongation of existing hospitalization **or**
3. Results in persistent or significant disability or incapacity **or**
4. Results in a congenital anomaly or birth defect **or**
5. Results in death **or**
6. Based upon appropriate medical judgment, it may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, **or**
7. Adversely affects the risk/benefit ratio of the study

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

Adverse Events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

The CTCAE uses a scale of **Grades 1 to 5**, with each grade corresponding to a level of severity:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (activities of daily living).
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.

- **Grade 5:** Death related to the adverse event.

For each specific adverse event, the CTCAE provides detailed criteria to determine the appropriate grade. This ensures consistency in reporting and allows for better comparison of safety data across different studies.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

Investigators examining and evaluating participants will assess the relationship of all adverse events (AEs) to the study intervention. This assessment will be based on the temporal relationship and the clinician's clinical judgment, with the degree of causality graded using the following categories.

ATTRIBUTION OF ADVERSE EVENTS

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures by the principal investigator according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).

b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).

c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).

d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).

e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

8.2.3.3 EXPECTEDNESS

The investigator and study team will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described for the study intervention.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by individuals that are delegated by the PI to assess event attribution), and time

of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is consented will be considered as baseline and not reported as an AE. However, if the study participant's condition changes or deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

PI delegated personnel will record all reportable events with start dates occurring any time after informed consent is obtained until the follow-up period as per the SoA. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.5 ADVERSE EVENT REPORTING

All Adverse Events must be reported in the appropriate CRF. After study completion, the follow-up period as per the SoA if assessed as reasonably related (possibly, probably, definitely) to protocol treatment.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the NHCI DSMC any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. To report the SAE to the NHCI DSMC, the investigator will complete the NHCI Medical Events Form and will submit the form with supporting documentation to NHCI-IITCore@northwell.edu.

Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the NHCI DSMC.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the investigator deems the event to be chronic, or the participant is stable. Other supporting documentation for the event may be requested by the NHCI and should be provided as soon as possible.

8.2.7 REPORTING OF PREGNANCY

Who CANNOT Participate in This Study:
Patients who are either pregnant, breastfeeding or actively trying to conceive are not eligible for this study since the study intervention poses both known and potential unknown risk to a fetus or newborn infant. Known risks of prenatal radiation exposure above 0.50 Gy include:

- Failure of embryonic implantation
- Higher likelihood of miscarriage
- Increased chance of major developmental malformations (such as neurological and motor deficiencies)
- Fetal growth restriction
- Neonatal demise

Contraception Requirements During Study Participation:
Due to the serious risks associated with radiation exposure, all participants of child-bearing potential and partners of childbearing potential must use reliable contraception throughout the entirety of the subject's study participation (i.e. from a minimum of four weeks prior to registration and continue without interruption until the completion of the final 2-year follow-up assessment). Acceptable forms of contraception include:

- Hormonal (such as oral contraceptive pills)
- Double-barrier (such as condoms with spermicide, contraceptive sponge with spermicide or diaphragm with spermicide)
- Complete Abstinence from Intercourse

What To Do if a Pregnancy Occurs:
Despite contraception requirements, any pregnancy that occurs in a study participant or their partner from the time of informed consent through 90 days after completing the study intervention must be reported to the NHCI DSMC and the IRB within 24 hours of discovery. Although pregnancy is not classified as an adverse event, study staff must complete the Pregnancy Information Form included in the NCI Guidelines for Adverse Event Reporting Requirements and follow the pregnancy through delivery to document the outcome. Any infant conceived while either parent was participating in the study must be followed until 30 days of age.

8.2.8 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied,
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2.9 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the NHCI DSMC and lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 5 days of becoming aware of the event and to the NHCI/study sponsor within 24 hours of the investigator becoming aware of the event.
- The investigator will report unanticipated problems (UPs) to the lead principal investigator (PI) and the NHCI DSMC within 24 hours of becoming aware of the event, and to the Institutional Review Board (IRB) of record within 5 business days of becoming aware of the event
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 14 business days of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  See below.

- Secondary Efficacy Endpoint(s):
  See below.

9.2 SAMPLE SIZE DETERMINATION

The proposed sample size for this study is 12 evaluable subjects (i.e., 12 patients who meet all eligibility criteria listed). The proposed sample size is based on feasibility and availability of resources. It is not based on any formal power calculations. Preliminary data generated from this study may be potentially useful to design and power a larger scale study (randomized clinical trial).

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

This is a pilot study and therefore, the statistical approach will be descriptive. In general, all continuous data will be summarized using descriptive statistics such as mean (SD) or median (IQR (interquartile range)), minimum and maximum. Categorical data, including one-year local recurrence, LMD and RN will be reported using frequency, proportions, and the associated 95% confidence intervals (CI). Graphical methods will be applied to visualize the trend in MoCA scores over time and compare the MoCA scores amongst the three timepoints. If sufficient follow-up is available, we will also estimate median survival time using the Kaplan-Meier product limit method. All statistical analyses will be performed using statistical software SAS v9.4 (SAS Institute, Inc., Cary, NC, USA).

9.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The rate of local (resection cavity) freedom from progression (FFP), defined as the absence of new nodular contrast enhancement 2 mm or less from the resection cavity, will be estimated at 6, 12, 18, and 24 months with corresponding 95% CIs, using the Kaplan-Meier product limit method. Censoring will occur at the last follow-up for patients without progression.

All secondary endpoints (MLD, RN, and neurocognitive function outcomes) will be analyzed using point estimates and exact two-sided Clopper Pearson 95% confidence intervals (CIs).

PFS and OS will be estimated using the Kaplan-Meier method and compared across pathologic subgroups and extent of surgical resection categories using the log-rank test. Univariable Cox proportional hazards regression models may also be used to evaluate associations between pathologic characteristics, extent of resection, and PFS and OS. Results will be reported using hazard ratios (HRs) with 95% CIs will be reported.

9.3.3 PLANNED INTERIM ANALYSES

No interim analyses will be conducted throughout the course of this pilot study to ensure the integrity and reliability of the final results.

9.3.4 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual Participant will be listed by measure and each time point.

9.4 SAFETY MONITORING AND STOPPING RULES

Accrual will be continuously monitored. If a boundary is triggered, accrual will pause immediately for review by the Principal Investigator and the Safety Monitoring Committee (SMC).

Toxicity Monitoring: Continuous toxicity monitoring will be conducted after each evaluable patient. Let X_n denote the cumulative number of patients experiencing a toxicity event among the first n evaluable patients. At each interim evaluation, X_n will be compared with the prespecified Pocock stopping

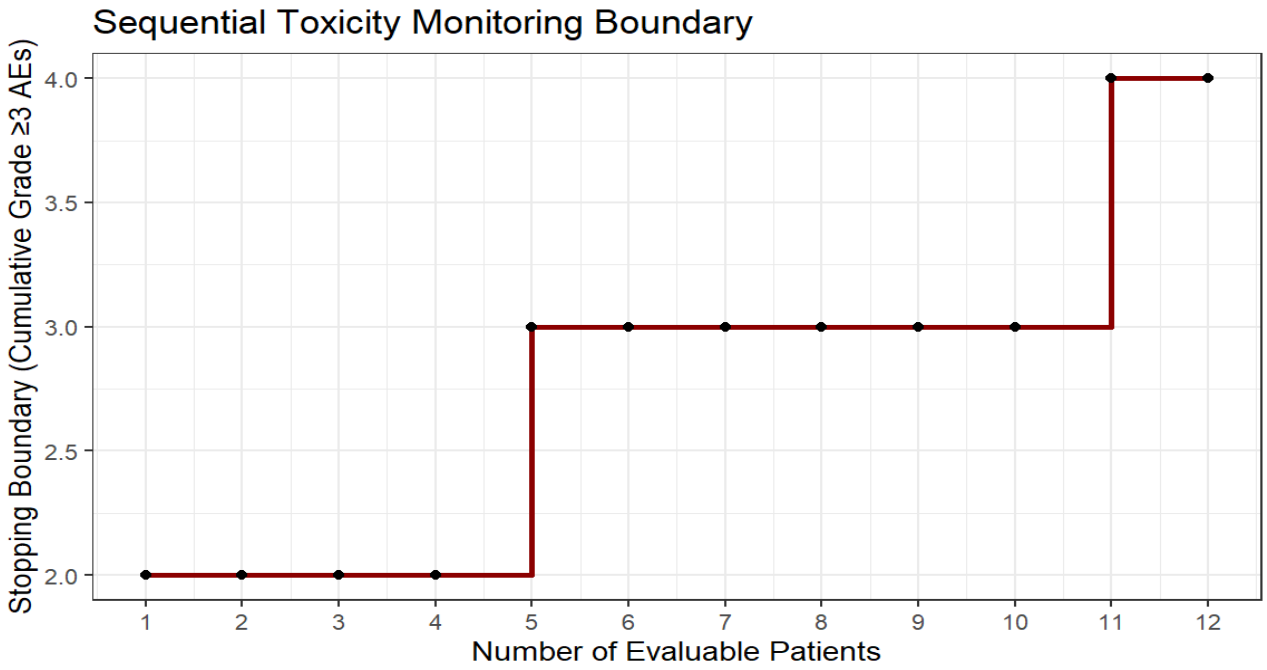
boundary. Accrual will be permanently suspended if the observed cumulative number of toxicity events equals or exceeds the boundary corresponding to the current number of evaluable patients; early stopping triggered if at least 2 toxicities are observed among the first 2-4 evaluable patients, at least 3 toxicities among 5-10 evaluable patients, or at least 4 toxicities among 11-12 evaluable patients (Table 1 and Figure 1). The sequential toxicity monitoring boundary was calibrated to control the overall one-sided type I error rate at approximately 10% when the true Grade ≥3 adverse event rate is 10%, while maintaining a high probability of early termination (78%) when the true toxicity rate is 35%. The probability of early termination and average sample size were evaluated across a range of true toxicity rates (Table 2).

Table 2: Pocock Sequential Monitoring Rule for Excessive Toxicity

Evaluable Patients	**Stop if grade ≥3 AEs ≥**
2-4	2
5-10	3
11-12	4

** Enrollment will be terminated if the cumulative number of grade ≥3 adverse events equals or exceeds the corresponding boundary at any time during continuous monitoring.*

Figure 1: Pocock Sequential Monitoring Rule for Excessive Toxicity



** The figure displays the cumulative number of grade ≥3 adverse events required to trigger study termination as a function of the number of evaluable patients. Continuous toxicity monitoring will be performed after each evaluable patient. Enrollment will be stopped if the cumulative number of grade ≥3 adverse events equals or exceeds the boundary shown.*

Table 3: Operating Characteristics of the Pocock-Type Sequential Monitoring Rule for Grade ≥3 Adverse Events

Toxicity Rate	Probability of Early Termination	Average Sample Size
0.05	0.022	11.85
0.10	0.098	11.40
0.20	0.373	9.77
0.25	0.527	8.78
0.30	0.667	7.78
0.35	0.780	6.83
0.40	0.866	5.98

** Probability of early termination denotes the probability that the study will stop for excessive toxicity before reaching the maximum sample size of 12 evaluable patients. Average sample size denotes the expected number of evaluable patients accrued under the assumed true toxicity rate.*

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Although recruitment for this study does not target non-English speaking patients, eligible non-English speaking patients will not be excluded from the study. Informed consent will be obtained using a translated Short Form and translated HIPAA authorization form in the language that the patient speaks, in addition to the IRB-approved English consent form, in accordance with the Northwell HRPP policies. The consent process will be conducted using an interpreter (either in-person or telephonic) in accordance with Northwell policies.

Enrollment of decisionally impaired patients will be allowed via consent by a legally authorized representative in accordance with HRPP policies. To determine a subject's capacity to consent for a research study, the PI and consenting sub-investigators will perform the decision-making capacity evaluation by documenting whether the subject can communicates his or her choice of being on the study, verbalizes understanding of risks and benefits of being on the study and can apply this to himself/herself. A determination of incapacity is made when the subject is unable to communicate the details of being on the study (as described above). The determination and cause will be clearly documented including the nature, cause, extent and probable duration in the subject's enrollment note. The individuals from whom permission will be obtained as a legally authorized representative in order of priority include a court appointed legal guardian, a court appointed health care agent and next of kin. Assent will also be obtained from subjects who require a legally authorized representative through a verbal method using an assent script. The investigator will document the subject's decision in the enrollment notes. If the subject displays any elements of dissent by word or gesture, the subject will not be enrolled on the trial. At future study visits, the PI and/or consenting sub-investigators will assess the subject's continued capacity and if capacity is regained the subject will be re-consented without a legally authorized representative.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of

the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements
- Data that is not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met.
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for at least two years or as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Northwell Health Cancer Institute. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NHCI CCTO research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NHCI REDCap.

10.1.4 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Northwell Health Cancer Institute Data and Safety Monitoring Committee (DSMC) composed of individuals with the appropriate expertise. Members of the DSMC that have a conflict-of-interest will abstain from voting on this study at scheduled safety review. Given the moderate risk level of this study, the DSMC will meet at least annually to assess safety and efficacy data. The DMSC will operate under the rules of an approved Data Safety and Monitoring Plan (DSMP). The DSMC determination will be provided to the NHCI Protocol Review and Monitoring Committee and to the Institutional Review Board per the approved Institutional Data and Safety Monitoring Plan.

10.1.5 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Safety and Data Monitoring for this study will be performed by the Northwell Health Cancer Institute Data and Safety Monitoring Committee (DSMC). The DSMC will assess data annually throughout the study. The DSMC co-chairs may call ad hoc meetings to address specific safety or efficacy concerns as they arise.
- Routine Risk Based Monitoring will be conducted quarterly. The frequency of routine monitoring may be decreased upon all participants entering the follow up period of a study in accordance with the stipulations of the NHCI DSMC SOP and with approval from the DSMC. Conversely, the frequency of routine monitoring may be increased should situations arise where there are safety, data integrity, or compliance concerns.
- The Principal Investigator (PI) will be provided copies of monitoring reports within 5 days of each monitoring visit.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted by Northwell Cancer Institute to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.6 DATA HANDLING AND RECORD KEEPING

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff under the supervision of the principal investigator. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap database, a 21 CFR Part 11-compliant data capture system provided by the NHCI CCTO. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appears inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.6.2 STUDY RECORDS RETENTION

All study documents must be kept for at least two years after the formal discontinuation of the study. No records should be destroyed without the Principal Investigator's (PI) explicit written consent. The PI is solely responsible for informing both the study team and the NHCI Cancer Clinical Trials Office when these documents can be destroyed.

10.1.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations in accordance with the IRB of record and NHCI CCTO policies. All deviations must be recorded on a study deviation log, reported to the IRB and the NHCI DSMC. The PI is responsible for knowing and adhering to the IRB, CCTO and NHCI DSMC requirements.

10.1.8 PUBLICATION AND DATA SHARING POLICY

This trial will be registered at ClinicalTrials.gov, and results and such information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. These publications will not contain any identifying information or any information that could be in any way linked to identifying information.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BM	Brain Metastasis
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTV	Clinical Target Volume
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFP	Freedom From Progression
FFR	Federal Financial Report
fSRS	Fractionated Stereotactic Radiosurgery
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GTV	Gross Tumor Volume
GWAS	Genome-Wide Association Studies
Gy	Gray (unit of radiation dose)
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization

ITT	Intention-To-Treat
KPS	Karnofsky Performance Status (KPS)
LMD	Leptomeningeal Metastatic Disease
LR	Local Reoccurrence
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OAR	Organ(s) at Risk
OHRP	Office for Human Research Protections
OS	Overall Survival
PFS	Progression-Free Survival
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RN	Radiation Necrosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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