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Official Title: A Pilot Study Analyzing Preoperative Stereotactic Radiosurgery (SRS) With Gamma Knife (GK) for Brain Metastases
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MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER

A Pilot Study Analyzing Preoperative Stereotactic Radiosurgery (SRS) with Gamma Knife® (GK) Icon™ for Brain Metastases

Short Title:

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Amber Retzlaff, MD (Co-PI)

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TITLE: A Pilot Study Analyzing Preoperative Stereotactic Radiosurgery (SRS) with Gamma Knife® (GK) Icon™ for Brain Metastases

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Funder:

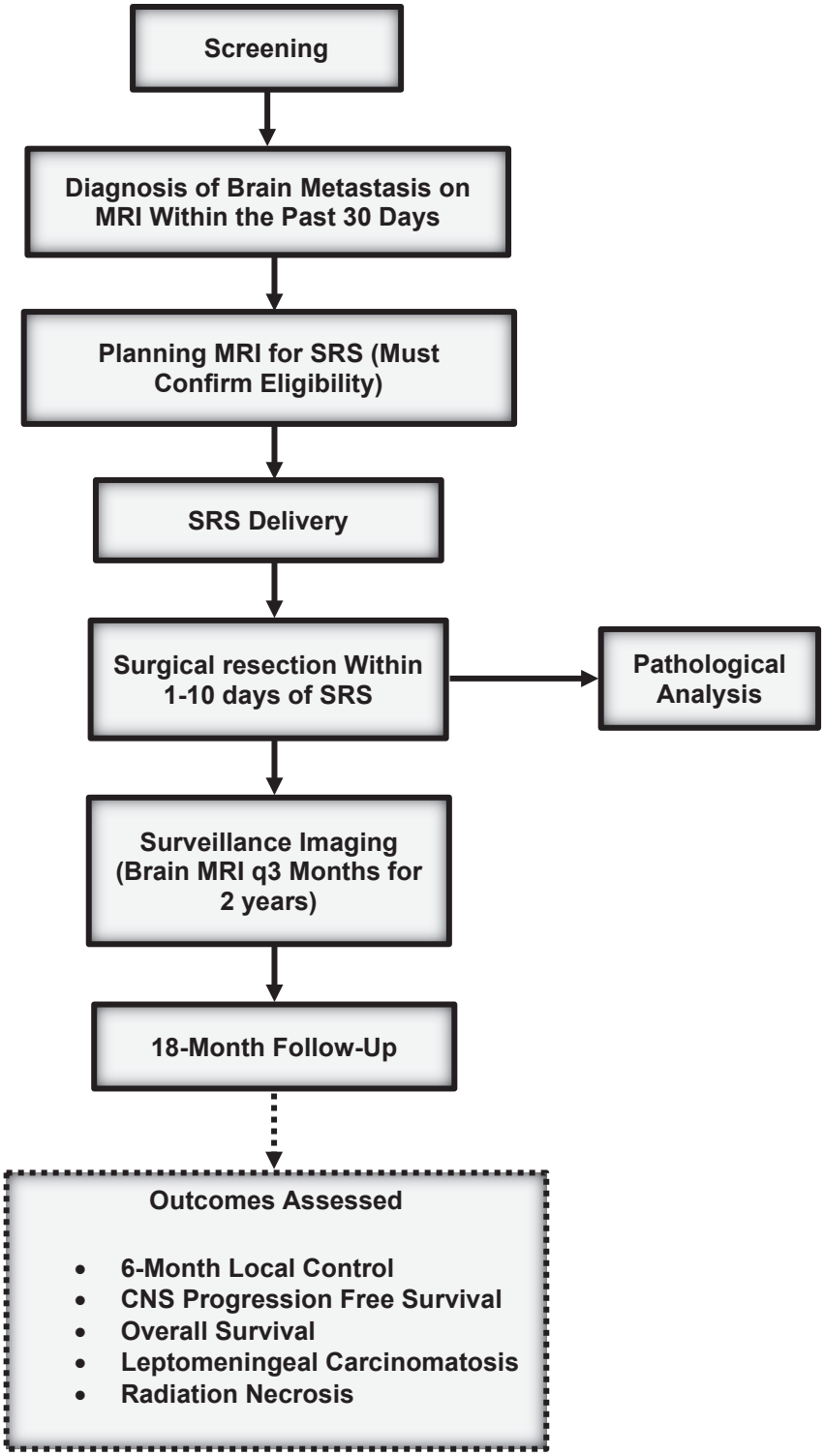
TABLE OF CONTENTS

PROTOCOL SUMMARY

Title	A Pilot Study Analyzing Preoperative Stereotactic Radiosurgery (SRS) With Gamma Knife® (GK) Icon™ for Brain Metastases
IND Sponsor	Not applicable
Principal Investigator	Michael Straza, MD
Study Population	Patients with radiographically confirmed solid tumor brain metastases.
Primary Objectives	1. To assess feasibility of preoperative GK-SRS in patients with brain metastases treated with preoperative GK-SRS. 2. To assess local control in patients with brain metastases treated with preoperative GK-SRS.
Primary Endpoint	1. Feasibility for this study will be defined as 50% of enrolled study subjects undergoing the surgical resection as per the protocol. 2. Measure the rate of local control at the resection cavity and the development of new metastatic brain tumors elsewhere in the brain as identified on post-treatment MRI of the brain.
Secondary Objectives	1. To assess survival (CNS progression-free survival and overall survival) for patients undergoing preoperative SRS and surgical resection. 2. To document rates of leptomeningeal carcinomatosis for patients undergoing preoperative SRS and surgical resection. 3. To record incidence of radiation necrosis in patients undergoing preoperative SRS and surgical resection. 4. To document quality of life measures using preoperative Gamma Knife® and to compare to historically cited rates using postoperative Gamma Knife®.
Secondary Endpoint	1. CNS progression-free survival and overall survival will be evaluated at six, 12, and 18 months after surgical resection. 2. Rates of leptomeningeal carcinomatosis using preoperative SRS will be documented and compared to historically cited rates for postoperative SRS. 3. Incidence of radiation necrosis will be measured by post-treatment MRI. 4. Quality of life measures will be collected and will be compared to historically cited rates.
Study Design	This is a single-arm, single-center, pilot study in which 10 completed patients with one to four brain metastases diagnosed on brain MRI within the past 30 days will be evaluated for study eligibility and enrolled as appropriate.
Study Intervention Description	Enrolled patients will receive SRS to all metastases followed by surgical resection of resectable metastases within one to 10 days following

	SRS. Pathologic specimens will be analyzed, and the patient will enter a standard pattern of surveillance (brain MRI every three months for two years).
Number of Subjects	Up to fifteen subjects will be enrolled in this study to attain ten completed subjects.
Estimated Time to Complete Enrollment:	Approximately two years.

STUDY SCHEMA



STUDY CALENDAR

Procedure	Screening[1]	Radiosurgery Delivery	Surgical Resection	Post-Surgical Resection Visit	Follow-up[2] (until 18-months from post-surgical resection visit) (18 months)
Study Day/Visit Day	**Day – 30 to Enrollment**	**Day 1**	**Day 2 (+8 days)**	**1-month ±7 days from radiosurgery**	**Every 3 months ±14 days**
Informed Consent	X				
AE Reporting	X	X	X	X	
Concomitant Medications	X	X	X	X	X
SRS		X			
Physical Exam[3]	X			X	X
Medical History	X				
ECOG Performance Status	X			X	X
Pregnancy Test (Serum or Urine)[4]	X				
Neurocognitive Testing[5]	X				Every 6 months± 14 days
QOL Questionnaire[6]	X			X	X
MRI (Brain)[7]	X			X	X

1. All screening procedures must occur within 30 days prior to enrollment. Treatment must start within 14 days of enrollment.
2. If a subject has disease progression/relapse or subject withdrawal, then they will be followed as per follow-up requirements.
3. Including height and weight on screening. Temperature, HR, RR, BP and O_2 sats or as per institutional standards at all timepoints.
4. For women of childbearing potential, a negative pregnancy test (serum or urine) must be obtained within 30 days prior to the first study intervention.
5. Neurocognitive testing: Multilingual Aphasia Examination Controlled Oral Word Associated Test (COWAT), Trail Making Test, Parts A and B (TMT), and Hopkins Verbal Learning Test-Revised (HVLT-R).
6. QOL Questionnaire: MDASI-BT, EQ-5D-5L.
7. MRI (brain) w/ contrast. Radiographic assessments will be completed as per RANO criteria (see Appendix 3).

LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	intravenous
LDH	lactate dehydrogenase
MCWCC	Medical College of Wisconsin Cancer Center
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	overall response rate
PD	disease progression
PK	pharmacokinetics
PO	per os (by mouth, orally)
PR	partial response
QOL	quality of life
SAE	serious adverse event
SD	stable disease
SD	standard deviation

SRC	Scientific Review Committee
ULN	upper limit of normal
UP	unanticipated problem
UPIRSO	unanticipated problems involving risks to subjects or others

1 BACKGROUND

1.1 Brain Metastases: Epidemiology and Prognostic Factors

Brain metastases are the most common intracranial malignancy in adults and occur in up to 30 to 40% of cancer patients.[1-7] Common primary etiologies include breast cancer, lung cancer, renal cell carcinoma, and melanoma.[2,5,7] Symptoms depend on specific intracranial location, tumor volume, mass effect, tumor histology, and tumor-related hemorrhage.[2] In general, prognosis after diagnosis of brain metastasis is poor; however, longer survival is now being observed with improved systemic therapies as well as earlier detection at more limited stages of neurologic involvement.[2,3,5,8,9] Favorable prognostic factors include young age (<60 years), good performance status, female gender, solitary metastasis, absence of neurologic symptoms, and well-controlled primary disease with absence of metastasis outside the central nervous system.[2,3,10,11]

1.2 Treatment Paradigm

Management is influenced by the number, location, and volume of brain metastases, as well as tumor histology, molecular markers, and recursive partitioning analysis (RPA) or graded prognostic assessment (GPA).[1,5] Historically, approaches that have been investigated for treatment of one to four brain metastases include surgery alone, whole-brain radiation therapy (WBRT) alone, WBRT followed by surgery, surgery followed by WBRT, and surgery followed by SRS.[1,5,11] Efficacy and timing of systemic treatment is an additional consideration for management of brain metastases depending on primary tumor histology.[5]

1.3 Historical Perspectives

Early studies by Patchell et al. demonstrated superior local control and overall survival with the addition of surgery to WBRT, as well as superior local control and lower rates of neurologic-related deaths with the addition of WBRT to surgery for treatment of solitary brain metastases.[12,13] A Cochran review published in 2005, however, did not confirm an overall survival benefit with the addition of surgery to WBRT.[2] As SRS was developed, studies began evaluating WBRT with SRS boost.[5] Collectively, these studies demonstrated a local control benefit using WBRT with SRS boost, as well as an overall survival benefit in patients with more favorable prognosis (favorable GPA, RPA Class 1, or solitary metastasis).[5,6,11,14,15]

Due to concerns related to cognitive decline and quality of life measures with WBRT, studies on the use of SRS alone for a limited number of brain metastases ensued.[5,6,11] These studies consistently reported superior local control and distant brain control with SRS plus WBRT compared to SRS alone, although conclusions related to overall survival were variable.[5,6,11,16-20] Aoyama et al. reported an overall survival benefit using SRS with WBRT only in those with higher GPA scores, while Chang et al. reported a superior overall survival with SRS alone.[5,17,18] Kocher et al., Brown et al., and Churilla et al. reported no difference in overall survival with the addition of WBRT.[19,21,22] A meta-analysis by Soon et al. concluded no difference in overall survival, while an individual patient-data meta-analysis by Sahgal et al. concluded that SRS alone provides a survival benefit for patients <50 years of age.[16,20,23] In addition, a recently published retrospective review comparing survival outcomes with SRS alone versus WBRT alone reported improved survival with SRS alone in patients with limited brain metastases from lung or breast cancer.[24]

1.4 Recurrence Patterns

Lesions >3 cc in size often require surgical intervention to relieve mass effect and neurologic symptoms.[6,13] Risk of recurrence at the resection cavity has been reported to be approximately 50%; consequently, postoperative radiation in the form of WBRT or SRS is frequently used to sterilize the surgical bed.[6,12,19] Prospective data to support superiority of SRS versus WBRT in the postoperative setting is lacking, although there is some retrospective evidence to suggest that postoperative WBRT provides better intracranial local control than postoperative SRS for larger brain metastases but with no difference in OS.[5,6] It should be noted that these comparisons are limited by the retrospective nature; in addition, optimal dose/fractionation schemes for postoperative SRS have not yet been determined with certainty.[6,7]

1.5 Toxicity

Multiple studies report worsened cognitive decline and quality of life with the addition of WBRT to either SRS or surgery for a limited number of brain metastases.[3,5,6,18,21,25] Given evidence for WBRT-related toxicity along with the lack of clear survival benefit with the addition of WBRT (and potentially a survival benefit with SRS alone in certain populations), the current trend for management of limited brain metastases now favors surgery (+/- postoperative SRS) or SRS alone with reservation of WBRT as a salvage option.[1,4-6,9,11] A number of studies are now evaluating the use of SRS in patients with multiple (more than four) brain metastases.[3-5,8,11,26,27] According to a recently published systematic review, SRS may be considered an option for patients with greater than four brain metastases provided the total tumor volume does not exceed 13 cc and no single metastasis is larger than 3 cc in volume.[1] While postoperative WBRT carries the cognitive and quality of life toxicities discussed above, SRS carries the risk of CNS necrosis (up to 23%).[28,29] In an effort to reduce the risk of radiation necrosis with SRS applied to larger volumes while retaining efficacy, different dose and fractionation schedules are under investigation.[6,7]

1.6 Leptomeningeal Carcinomatosis

With increased utilization of postoperative SRS in place of WBRT and expanding data on outcomes, specific patterns of CNS failure are becoming clearer. A number of studies report excellent local control rates with postoperative SRS (up to 83 to 94% at 24 months) but with distant intracranial failure rates of 40 to 60% within 12 months.[28,30] This is consistent with previously published data demonstrating inferior distant brain control with SRS compared to SRS with adjuvant WBRT.[5,6,11,16-19]

Of increasing interest is the incidence of leptomeningeal carcinomatosis in patients with solid tumors and brain metastases. Rates of leptomeningeal disease with solid tumors are reported to be in the range of 5 to 15%. Risk factors for leptomeningeal involvement include breast cancer histology (particularly triple-negative receptor status and infiltrating lobular carcinoma), as well as non-small cell lung cancer and melanoma histologies.[31,32] Treatment options at the time of leptomeningeal failure typically include radiation, intrathecal chemotherapy, and/or systemic chemotherapy depending on histology.[9,32] Prognosis with leptomeningeal metastasis is poor, with reported survival in the range of two to six months.[9,16,31,32]

Neurosurgical risk factors for leptomeningeal carcinomatosis include piecemeal resection, opening of the ventricular system, and infratentorial lesions.[31,33] In the setting of up-front surgery, the hypothesis is that any anatomic disruption that allows cerebrospinal fluid (CSF) contamination with tumor cells may predispose for leptomeningeal spread.[9,29-31,34] Although postoperative SRS

provides excellent local control at the resection cavity, it does not address tumor cells that have seeded the CSF. Currently reported rates of leptomeningeal failure after surgery with postoperative SRS for brain metastases are in the range of 8 to 24%.[33]

In 2016, Johnson et al. reported significantly greater incidence of leptomeningeal metastasis with surgery followed by SRS in comparison to SRS alone (16.9% vs. 5.2%, p<.01).[9] Ma et al. published similar findings, reporting a 6.5 times higher odds of leptomeningeal disease in patients who were treated with surgical resection prior to SRS.[32] A recently published abstract by Prabhu et al. describes a "nodular" pattern of leptomeningeal spread associated with surgery followed by SRS that is distinct from the classic "sugarcoated" pattern of leptomeningeal carcinomatosis described in other settings.[29] The authors also reported more favorable survival with the nodular pattern and that SRS may be a feasible option for focal treatment of nodular leptomeningeal disease.[29] Adjuvant WBRT may offset the risk of leptomeningeal disease some degree, although this does not address the entire volume of CSF circulation.[9,32]

1.7 Study Rationale

Given the increased risk of leptomeningeal failure with surgery followed by SRS, as well as the risk of radiation necrosis, new paradigms in therapy delivery and sequencing are being explored.[29,33-35] Areas of investigation include optimization of target volume, marginal expansion, multifractionation, timeliness of SRS after surgery, and delivery of SRS prior to surgical resection.[33,34] In theory, advantages of preoperative SRS include better target delineation, sterilization of tumor cells prior to surgical disruption of the tumor, vascular supply, and CSF spaces, and resection of tissue that would otherwise be at risk of radiation necrosis.[29,34,35]

In 2014, Asher et al. reported that the use of neoadjuvant SRS prior to surgery was both safe and effective (even for metastases >3 cm) with no reported leptomeningeal recurrences or radiation necrosis.[34] More recently, Patel et al. performed a retrospective comparison of preoperative versus postoperative SRS and reported no difference in local control, distant brain failure, or overall survival. Furthermore, the authors reported significantly lower rates of leptomeningeal carcinomatosis and radiation necrosis with preoperative SRS.[29,36]

Huff et al. recently published a protocol for a phase II prospective trial designed to compare outcomes using preoperative SRS versus historically cited outcomes for postoperative SRS.[28] Our current pilot study mirrors this design and aims to confirm study feasibility and to assess local control, CNS progression-free survival, overall survival, rates of leptomeningeal spread, rates of radiation necrosis, and quality of life measures with the use of preoperative SRS.

2 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

Our hypothesis is that preoperative GK-SRS is feasible and results in greater local control than postoperative radiosurgery to the resection cavity.

2.1 Primary Objectives

1. To assess feasibility of preoperative GK-SRS in patients with brain metastases treated with preoperative GK-SRS.
2. To assess local control in patients with brain metastases treated with preoperative GK-SRS.

2.2 Secondary Objective(s)

1. To assess survival (CNS progression-free survival and overall survival) for patients undergoing preoperative SRS and surgical resection.
2. To document rates of leptomeningeal carcinomatosis for patients undergoing preoperative SRS and surgical resection.
3. To record incidence of radiation necrosis in patients undergoing preoperative GK-SRS and surgical resection.
4. To document quality of life measures using preoperative GK-SRS and to compare to historically cited rates using postoperative GK-SRS.

2.3 Primary Endpoint

1. Feasibility for this study will be defined as 50% of enrolled study subjects undergoing the surgical resection as per the protocol.
2. Measure rate of local control at the resection cavity any new tumors by post-treatment MRI.

2.4 Secondary Endpoint(s)

1. CNS progression-free survival and overall survival will be evaluated at six, 12, and 18 months following surgical resection.
2. Rates of leptomeningeal carcinomatosis using preoperative GK-SRS will be documented and compared to historically cited rates for postoperative GK-SRS.
3. Incidence of radiation necrosis will be measured by post-treatment MRI.
4. Quality of life measures will be collected and will be compared to historically cited data.

3 STUDY DESIGN

3.1 General Description

This is a single-arm, single-center, pilot study in which 10 completed patients with one to four brain metastases diagnosed on brain MRI within the past 30 days will be evaluated for study eligibility and enrolled as appropriate.

3.2 Design of the Current Study

Enrolled patients will receive GK-SRS to all metastases followed by surgical resection of resectable metastases within one to10 days following GK-SRS. Pathologic specimens will be analyzed, and the patient will enter a standard pattern of surveillance (brain MRI every three months for two years).

Quality of life will be assessed every three months, and neurocognitive evaluations will be performed every six months. These parameters will be compared to baseline testing performed at the time of enrollment. Local control, CNS progression-free survival, overall survival, rates of leptomeningeal carcinomatosis, rates of radiation necrosis, and steroid requirements will also be documented and compared with historically reported rates.

3.3 Estimated Time for Completion of Study Enrollment

Approximately two years.

4 SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

MCW must follow all MCW IRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: pre-consent (subject considering trial or study staff considering patient for the trial per institutional recruitment methods).
- Screening: period after consent, but prior to eligibility confirmation.
- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibly criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first day treatment was given to the last day treatment was given.
- Off treatment: the last day treatment was given.
- On follow-up: from last day of treatment to the end of follow-up period.
- Off study: follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local principal investigator.

4.2 Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent but are not subsequently assigned to the study intervention or enrolled in the study. MCWCC CTO will follow its SOPs regarding prescreening and screening tracking.

4.3 Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific

assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record (per local IRB policies and SOPs). The original will be kept on file with the study records.

4.4 Screening Procedures

Refer to the study calendar of events.

Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window.

4.5 Eligibility Confirmation

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

No waivers of protocol eligibility will be granted. When clinical factors relating to an eligibility item are unclear or questionable, the study PI (Michael Straza, mstraza@mcw.edu) can only provide guidance or clarification on eligibility.

Inclusion Criteria

1. Voluntary written consent must be given before performance of any study-related procedure that is not part of standard medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
2. English speaking.
3. Female or male subject's ≥ 18 years old at the time of informed consent.
4. Radiographically confirmed solid tumor brain metastases.
5. Criteria for surgical resection of at least one metastasis per neurosurgeon discretion.
6. Stereotactic radiosurgery candidate per radiation oncologist discretion.
7. A diagnostic MRI brain or CT head demonstrating the presence of one to four solid tumor brain metastases and lesion to be resected no more than 5 cm in any direction, performed within 30 days prior to stereotactic radiosurgery.
8. For known and unknown primary, ds-GPA estimated median survival no less than six months.
9. Surgical resection able to be performed within one to 10 days after radiosurgery.
10. Patients currently on cytotoxic chemotherapy or immunotherapy are eligible, not including anti-VEGF therapy.
11. Female subjects who:
    a. Are postmenopausal for at least one year before the screening visit, OR
    b. Are surgically sterile, OR

If they are of childbearing potential:

i. Agree to practice one highly effective method and one additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through four months after the last study Intervention (female and male condoms should not be used together), OR

ii. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

CRC Initials: _____ Date: _____

Investigator/Enrolling Physician Initials: _____ Date: _____

12. Male subjects, even if surgically sterilized (i.e., status post-vasectomy), who:
    a. Agree to practice effective barrier contraception during the entire study treatment period from the time of signing the informed consent through and through four months after the last study intervention (female and male condoms should not be used together), OR
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Exclusion Criteria

1. Patients who received anti-VEGF therapy within six weeks prior to enrollment, as there is increased risk of fatal brain hemorrhage with surgical resection.
2. Non-English speaking.
3. Major medical illnesses or psychiatric impairments, which in the investigator's opinion will prevent administration or completion of the protocol therapy and/or interfere with surveillance.
4. Patients with more than four brain metastases on MRI brain.
5. Lesion to be resected is more than 5 cm in any dimension.
6. Patients with leptomeningeal metastases documented by MRI or CSF evaluation.
7. Previous whole-brain radiation therapy.
8. Previous radiation therapy to the lesion to be resected.
9. Planned adjuvant focal therapy including additional radiation therapy to the brain.
10. Not a surgical candidate per neurosurgeon discretion.
11. Not a stereotactic radiosurgery candidate per radiation oncologist discretion.
12. Surgery unable to be performed between one to 10 days after radiosurgery.
13. Women who are pregnant or nursing as treatment involves unforeseeable risks to the fetus or child.
14. Patients who have a known or unknown primary and have an estimated median survival of less than six months per ds-GPA.

"I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible."

_____ _____
(CRC Signature) (Date)

_____ _____
(Investigator/Enrolling Physician Signature) (Date)

4.6 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. Subject will be considered in follow-up; study procedures should still be completed as indicated by the study protocol and AEs/SAEs will continue to be reported according to this protocol.

In the absence of treatment delays due to adverse events, study treatment/intervention may continue until:

- Disease progression.
- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- Intercurrent illness that prevents further treatment administration.
- Subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s) and/or dose level reduction beyond requirements as detailed in this protocol.
- Study stopping rules are met.

Subjects who sign the informed consent form, and are enrolled and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Consent Withdrawal

A subject may decide to withdraw from the study at any time. MCWCC CTO will follow its IRB of record's SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal with no study follow-up.
- Selective consent withdrawal from interventional portion of the study but agree to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

4.7 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
    - Three telephone calls (at least one day apart) from the study team are unanswered
      AND
    - A letter to the participant's last known mailing address goes unanswered (refer to Appendix 2).
      AND
    - These contact attempts must be documented in the participant's medical record or study file.
- Update OnCore® (follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the participating site study team, the subject should be considered in follow-up again.

4.8 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

- OnCore® tracks accrual throughout the study.
- If the study must be suspended, OnCore® is updated to a "suspended" status.
- When the accrual number is reached, OnCore® notifies staff of study closure.

4.9 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 the last scheduled procedure shown in the calendar of events or has been discontinued.

4.10 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study principal investigator, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB) and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

5 TREATMENT PLAN

5.1 Intervention Description

Guidelines for treatment based on tumor diameter (in cm)	
Maximum Tumor Diameter	Prescribed Dose
≤ 2 cm	20–24 Gy
2.1–3.0 cm	18 Gy
3.1–5.0 cm	15 Gy
SRS followed by surgery within one to 10 days. • A typical SRS dose of 20 Gy applied to one to four brain metastases provides local control of approximately 90%. • 15 Gy to 18 Gy = threefold increase in local failure compared to 24 Gy.	

5.1.1 Stereotactic Radiosurgery

SRS will be delivered utilizing Gamma Knife®. Target volume and isocenter determination will be based on a brain MRI with the patient's head in the stereotactic frame or face mask. SRS will be delivered to each lesion that has not previously undergone treatment. Due to the volumetric summation constraint for the remaining metastases, no single, non-resected lesion greater than 5 cm will be allowed in the study.

If any two lesions are within 0.8 to 2 cm of each other, the intervening midplane dose will not exceed 15 Gy. This may require treating each respective target with a lesser dose than dictated by the above dosing criteria to minimize toxicity. The dose to the critical structures, including optic pathway, brainstem, cochlea, and medulla, must meet constraints as determined by the radiation oncologist. If the above constraints cannot be met utilizing the prescribed radiosurgery dose, then the highest dose to the target volume will be used such that constraints can be met. This will be considered a minor deviation.

Possible Side Effects Related to Stereotactic Radiosurgery (SRS)

Common, Some May Be Serious
In 100 people receiving SRS, more than 20 and up to 100 may have:
Temporary (short-term) pain from with the head frame placement (if a head frame is used).

Occasional, Some May Be Serious
In 100 people receiving SRS, from four to 20 may have:

- Headache
- Localized hair loss which may be permanent
- Nausea

- Vomiting
- Allergic reaction to the local anesthesia (rash, itching, nausea, or difficulty breathing)
- Bleeding and/or infection around the head frame (if a head frame is used)
- Swelling of the brain in the treated area which may require treatment with steroids
- Severe local damage to or death of normal brain tissue, which may require surgery to remove

Rare and Serious

- In 100 people receiving SRS, three or fewer may have:
- Decreased brain function such as motor function (coordination/movement)
- Hardening of the arteries in the brain which rarely may lead to strokes many years after stereotactic radiosurgery
- A second new cancer caused by radiation, in the brain or nearby organs which rarely may occur many years after stereotactic radiosurgery
- Damage to vision tracts (eye damage) with the possibility of permanent blindness

Long-term effects of the radiation or radiosurgery used in this study include an increased risk of developing other cancers.

5.1.2 Surgical Resection

At least one of the four lesions must be either larger than 3 cm or symptomatic to meet the surgical resection criteria. One to 10 days after radiosurgery, the dominant lesion(s) will be maximally resected and labeled tissue will be sent to the neuropathology department for clinical diagnosis and radiobiological correlative studies. If for safety concern or other considerations, gross total resection is not reached, the residual disease in the setting of subtotal resection will be closely observed given that it has been treated with a definitive dose of SRS, reserving salvage local therapy for cases of progression.

Possible Side Effects Related to Surgical Resection

Common, Some May Be Serious

In 100 people receiving neurosurgery 20 to up to 90 patients may have:

- Pain
- Headache
- Nausea
- Vomiting

Occasional, Some May Be Serious

In 100 people receiving neurosurgery, 15 to up to 20 patients may have:

- Bleeding
- Infection

Rare and Serious

In 100 people receiving neurosurgery, less than five patients may have:

- Stroke
- Permanent injury, i.e., arms and legs not functioning properly, issues with speech
- Complications from anesthesia, i.e., heart or lung problems

6 ADVERSE EVENTS: DEFINITIONS, COLLECTION AND REPORTING REQUIREMENTS

6.1 Definitions

6.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonisation [ICH], E2A, E6).

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

6.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.

- **Life-threatening**. Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- **Pregnancy**

- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. 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; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

6.1.3 Attribution of an Adverse Event

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:

Definitely Related: *The AE is clearly related to the intervention*. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably Related: *The AE is likely related to the intervention.* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly Related: *The AE may be related to the intervention.* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Unlikely: *The AE is doubtfully related to the intervention.* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: *The AE is clearly NOT related to the intervention.* The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

6.1.4 Expectedness of an Adverse Event

Study investigator or treating physician will be responsible for determining whether an AE is expected or unexpected as indicated in the protocol, informed consent form and/or drug information brochure. An AE will be considered unexpected if the nature, severity, or frequency of the event is NOT consistent with the risk information previously described for the study intervention.

6.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

6.2.1 Collection of Adverse Events

All grade 3, 4, and 5 adverse events (including all SAEs) must be recorded in OnCore® and/or an adverse event log. All AEs required to be collected must be graded according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Investigator's or treating physician's assessment of AE attributions must also be documented.

AEs will be collected from the time the subject signs the consent form through 30 days post last dose of study drug(s). AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic.

Please see section 6.2.2 and table 2 to identify the adverse events that need to be reported.

6.2.2 Reporting of Adverse Events and Serious Adverse Events

Please refer to table 2 below to identify adverse events that meet reporting requirements.

All serious adverse events (SAEs) that occur after the subject has signed the consent form through 30 days post last dose of study drug(s) will be reported. All SAEs will be followed until satisfactory resolution, or until the investigator deems the event to be chronic.

All serious adverse events (SAEs) must also be documented in OnCore®.

Table 2

<table>
<tr><th rowspan="3">Attribution</th><th colspan="4">SAE</th><th colspan="3">AE</th></tr>
<tr><th colspan="2">Grade 1, 2 & 3</th><th colspan="2">Grade 4 and 5</th><th>Grade 3</th><th colspan="2">Grade 4</th></tr>
<tr><th>Expected</th><th>Unexpected</th><th>Expected</th><th>Unexpected</th><th>Unexpected</th><th>Expected</th><th>Unexpected</th></tr>
<tr><td>Unrelated
Unlikely</td><td rowspan="2">IRB[1] and DSMC[2]-Routine Review[3]</td><td>IRB[1] and DSMC[2]-Routine Review[3]</td><td rowspan="2">IRB[1]-Routine Review[3]

DSMC[2]-Within 5 calendar days</td><td>IRB[1]-Routine Review[3]

DSMC[2]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Routine Review[3]</td><td rowspan="2">DSMC[2]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Within 5 calendar days</td></tr>
<tr><td>Possible
Probable
Definite</td><td>IRB[1] and DSMC[2]-Within 5 calendar days</td><td>IRB[1] and DSMC[2]-Within 5 calendar days</td></tr>
</table>

1. Guidance on Adverse Event Reporting to the IRB is available online at MCW IRB Policies and Procedures.
2. For expedited DSMC reporting, study coordinator/research nurse must notify the DSMC via email including the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. DSMC will review data entered into OnCore®.
3. For routine reporting, the events will be reported to IRB as part of the annual continuing progress report and the DSMC will review data entered into OnCore® at the time of scheduled monitoring.

6.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website.

6.4 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

A product complaint is a verbal, written or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the drug manufacturer and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a drug manufacturer representative. Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed.

7 STATISTICAL CONSIDERATIONS

7.1 Power Calculations

The primary objective of this study is to demonstrate feasibility. With about 10 patients, assuming a local control of rate of 85% (in line with observed local control rates in the literature in 2014, Asher et al. and 2016, Patel et al.), [34,36] we will be able to estimate a 95% confidence interval with width not exceeding 0.40, that is about 47% of the assumed 85% local control rate.

7.2 Methodology of comparisons between groups

Descriptive statistics, including means, medians, and ranges will be reported wherever appropriate. For the primary hypothesis, the estimated rates of local control and its 95% confidence interval using an exact binomial method will be computed. For the secondary objectives, appropriate Kaplan Meier progression-free survival estimates will be computed.

All calculations will be performed using the SAS and the R language for statistical computing. Unless explicitly mentioned, all analysis will use a type I error rate of 0.05 and 95% confidence intervals.

7.3 Missing data and interim stopping

If patients do not complete the follow-up period, patients will be considered lost to attrition and their data will not be used for the primary or secondary objectives, except possibly for demographic descriptions. No missing data imputation or specific analysis is planned for this study. Since the primary objectives of this study are to study feasibility rather than evaluate efficacy or futility – early stopping is not meaningful in the present context. No stopping rules or interim evaluations are planned for this study.

8 DATA AND SAFETY MONITORING PLAN (DSMP)

Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data and Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with safety and progress reports submitted to the DSMC.

The DSMP for this study will involve the following entities:

8.1 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist and the study biostatistician. While subjects are on study, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings, including attendance, are documented.

8.2 Quality Assurance

This protocol was classified as high risk and will be reviewed internally by the MCW Cancer Center Clinical Trials Office Quality Assurance Staff according to the MCWCC Data and Safety Monitoring Plan and current version SOP, 6.5.2 Internal Quality Assurance Reviews.

8.3 Clinical Trials Office

The MCWCC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC.

8.4 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website (Data and Safety Monitoring Plan).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for patients.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports

from the study PI twice annually (review frequency may change based on study risk per DSMC discretion) and provide recommendations on trial continuation, suspension or termination, as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

9 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

9.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

9.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.3 Prestudy Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form and any other information pertaining to participants must be approved by the MCW IRB.

9.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

Informed Consent Process

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. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Potential subjects will be told, and a statement will be included that this study is designed to determine both safety and effectiveness. The consent forms will include the approved MCW IRB template language.

Consent forms will be IRB approved and the subject (and legally authorized representative, if necessary) will be asked to read and review the document. The treating physician or the investigator will explain the research study to the subject and answer any questions that may arise. The study coordinator may complete the consenting process. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., “Although not required, the subject’s spouse was present during the consenting process and signed as the witness.” Or “Although not required, hospital staff was present for consenting process and signed as a witness.”)

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects 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. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients who require reconsenting will be defined in the IRB-approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB’s policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject’s visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject’s satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent was given to the subject. The original consent is kept with the subject’s study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

9.5 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff, and the sponsor. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

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 principal investigator.

The conditions for maintaining confidentiality of the subjects’ records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked clinical research office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the case report forms contain the study identifiers, subject initials, date of birth and date of service.

Personal identifiers, such as name and medical record number, will be removed from accompanying lab reports and test results. Any data/PHI that are not stored for the purposes of the study are shredded in the Clinical Trials Office.

After all study queries and analyses are completed, the data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study.

9.6 Protection of Human Subjects

9.6.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

9.6.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

9.7 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

9.8 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

10 DATA HANDLING AND RECORD KEEPING

10.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

10.2 Data Management Responsibilities

10.2.1 Principal Investigator
The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication and investigational product(s), measurements, exams, evaluations and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.**

10.2.2 Research Coordinator
A research coordinator creates, collects and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

10.2.3 Research Nurse/Medical Staff
The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events and compliance to study procedures.

10.2.4 Biostatistician

The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

10.3 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file.

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

10.4 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific case report forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The clinical research coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The principal investigator will

approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

10.5 Study Record Retention

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on everyone administered the investigational intervention or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all predisease performance without restriction	100	Normal, no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do active work
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities; up and about more than 50% of waking hours	60	Requires occasional assistance but is able to care for most of personal needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization indicated although death not imminent
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20	Very ill; hospitalization indicated Although death not imminent
		10	Moribund
5	Dead	0	Dead

APPENDIX 2. LOST TO FOLLOW-UP LETTER

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial (A Pilot Study Analyzing Pre-Operative Stereotactic Radiosurgery (SRS) With Gamma Knife® (GK) IconTM for Brain Metastases) in which you participated.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at
_____

Sincerely,

_____

APPENDIX 3. RESPONSE CRITERIA FOR CNS METASTASES PROPOSED BY RANO-BM[37]

	Complete Response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion(s)†	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

*Progression occurs when this criterion is met.

†A new lesion is one that does not present on prior scans and is visible in a minimum of two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression.

‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

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