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Review

Radiosurgery dose reduction for brain metastases on immunotherapy (RADREMI): A prospective phase I study protocol

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ABSTRACT

Introduction: Up to 20% of patients with brain metastases treated with immune checkpoint inhibitor (ICI) therapy and concomitant stereotactic radiosurgery (SRS) suffer from symptomatic radiation necrosis. The goal of this study is to evaluate Radiosurgery Dose Reduction for Brain Metastases on Immunotherapy (RADREMI) on six-month symptomatic radiation necrosis rates.
Methods: This study is a prospective single arm Phase I pilot study which will recruit patients with brain metastases receiving ICI delivered within 30 days before SRS. All patients will be treated with RADREMI dosing, which involves SRS doses of 18 Gy for 0–2 cm lesions, 14 Gy for 2.1–3 cm lesions, and 12 Gy for 3.1–4 cm lesions. All patients will be monitored for six-month symptomatic radiation necrosis (defined as a six-month rate of clinical symptomatology requiring steroid administration and/or operative intervention concomitant with imaging findings consistent with radiation necrosis) and six-month local control. We expect that RADREMI dosing will significantly reduce the symptomatic radiation necrosis rate of concomitant SRS + ICI without significantly sacrificing the local control obtained by the present RTOG 90–05 SRS dosing schema. Local control will be defined according to the Response Assessment in Neuro-Oncology (RANO) criteria.
Discussion: This study is the first prospective trial to investigate the safety of dose-reduced SRS in treatment of brain metastases with concomitant ICI. The findings should provide fertile soil for future multi-institutional collaborative efficacy trials of RADREMI dosing for this patient population.
Trial Registration: Clinicaltrials.gov identifier: NCT04047602 (registration date: July 25, 2019).

1. Background & rationale

1.1. Epidemiology

Occurring ten times more frequently than primary brain tumors, brain metastases are by far the most common intracranial malignancy.[1] Associated with a median overall survival of 4–5 months, brain metastases afflict more than 200,000 people annually in the United States, comprising up to 30% of adults with cancer.[2–5]

1.2. Treatment of brain metastases

In general, treatment of metastatic brain disease involves surgical resection, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and/or systemic therapy. While conventional systemic therapies alone are typically not sufficient to control intracranial disease due to the presence of the blood-brain barrier, newer studies suggest efficacy of immunotherapy – predominantly via immune checkpoint inhibitors (ICI). Recent Level I evidence in patients with metastatic melanoma indicates that the 6-month local control rate of brain metastases treated with multi-agent ICI alone (nivolumab + ipilimumab) is 57%,[6] compared to the 24% rate of ipilimumab alone,[7] the 22% rate of pembrolizumab alone,[8] or the 50% rate of ipilimumab + fotemustine.[9] While the local control rate of multi-agent ICI is encouraging, it is important to remem-

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ber that the 57% rate remains vastly inferior to the six-month local control rates of 87-91% achieved following single-fraction SRS administered via linear accelerator or Gamma Knife.[6,10–12] Candidates for SRS are typically patients with 1–10 brain metastases, while patients exceeding 10 brain metastases often receive WBRT instead of SRS.[13]

1.3. Morbidity of standard-dose stereotactic radiosurgery + Immunotherapy for metastatic brain disease

A potential late toxicity of high-dose SRS for brain metastases is symptomatic radiation necrosis, which is associated with focal inflammation and intracranial edema at the irradiated site, often requiring steroid treatment (which is in itself counterproductive for optimizing efficacy of ICI) and/or craniotomy for resection of the necrosis in situations where the edema manifests as acute and potentially life-threatening neurologic deterioration.[14] Albeit limited compared to the addition of SRS, the efficacy of multi-agent ICI alone in achieving local control of more than half of brain metastases (including a 26% complete response rate) at six months brings forth an important question: Are the doses of SRS currently being administered for brain metastases excessive given that a large proportion of the metastatic brain disease population is receiving systemic ICI treatment?

Prior to the widespread use of immunotherapy, the radiographic radiation necrosis rate of SRS for metastatic brain disease was less than 5% (with the symptomatic radiation necrosis rate less than 3%); however, a recent large study of 115 patients has indicated that in the current immunotherapy era, the true rate of symptomatic radiation necrosis with SRS + ICI is as high as 20%.[15] Unfortunately, studies examining SRS + ICI have rarely reported radiation necrosis rates, and the vast majority of those doing so have failed to report symptomatic radiation necrosis rates.[16–20] Only two studies have reported symptomatic radiation necrosis rates, revealing a range from 12-20% of treated patients.[15,21] Unlike the majority of studies examining SRS + ICI, these two studies allow for determination of symptomatic radiation necrosis rates per patient rather than per treated lesion; for disease where it is common for patients to require treatment for multiple lesions, rates determined per patient will be substantially higher than those determined per treated lesion.

This is not a trivial consideration, as up to 1 in 5 patients treated with SRS for metastatic brain disease may develop symptomatic radionecrosis. This toxicity has the potential to affect outcomes in this patient population, given the proven association between steroid use and poorer overall survival for patients on ICI,[14] and the side effect profile of bevacizumab when used to address symptoms. The paucity of studies examining symptomatic radiation necrosis following SRS in brain metastasis patients who are receiving immunotherapy is further exacerbated by the lack of detail in the literature regarding radionecrosis rates relative to immunotherapy and SRS administration, and the dearth of prospectively collected data.[22] To date, only one study has reported the time from SRS to radiographic radiation necrosis rate (median: 14.7 months), with no studies reporting the time from SRS to symptomatic radiation necrosis.[21]

1.4. Proposed solution to metastatic brain disease treatment-related morbidity

A potential solution to this problem involves dose-reduced SRS to a level which substantially reduces radionecrosis risk without sacrificing the approximately 80-85% six-month local control provided by the present dosing schema, which from RTOG 90-05 has remained 24 Gy for lesions 0−2 cm, 18 Gy for lesions 2.1−3 cm, and 15 Gy for lesions 3−4 cm.[23]

To maintain a dosing schema less toxic than the RTOG 90-05 regimen while remaining within SRS doses established by Level I evidence to provide local control,[24] we propose the following dose-reduced SRS protocol for this *Ra*diosurgery *D*ose *Re*duction for Brain *M*etastases on *I*mmunotherapy (RADREMI) prospective pilot study: 18 Gy (0−2 cm lesions), 14 Gy (2.1−3 cm lesions), and 12 Gy (3−4 cm lesions) for brain metastases patients receiving at least one immunotherapy agent. These doses are consistent with Level I evidence comparing SRS with whole brain radiation therapy for metastatic brain disease, which revealed that SRS doses of 12−20 Gy were sufficient to provide local control.[24] For perspective, it is important to remember that RTOG 90-05 was not a dose finding study, but rather a dose tolerance study; subsequent work has established improved local control compared to RTOG 90-05 while using lower doses than the RTOG 90-05 regimen.[25–26] Given the efficacy of immunotherapy alone in treating melanoma brain metastases,[6] it is reasonable to hypothesize that a lower SRS dose than the RTOG 90-05 schema will result in a combinatorial effect sufficient to provide local control without resulting in the 20% symptomatic necrosis rate seen with the present dosing schema.[15]

1.5. Summary and rationale

In summary, this study seeks to assess the efficacy and safety of radiosurgery dose reduction for brain metastases patients receiving immunotherapy. We hypothesize that: 1. Dose-reduced SRS will reduce the risk of radionecrosis compared to the 16% average rate per patient from the existing concurrent SRS + ICI literature[15,21] with current SRS dose, and 2. Dose-reduced SRS will demonstrate non-inferior efficacy (measured primarily through six-month local tumor control) compared to the 90% local control rate associated with the RTOG 90-05-established SRS dosing parameters. For the purposes of this study, radionecrosis will be defined as clinical symptomatology following SRS requiring steroid utilization and/or operative intervention in combination with imaging features strongly suggesting radionecrosis as demonstrated utilizing routine MRI, MR Perfusion, MR Spectroscopy, and/or PET imaging. Although the definition of concurrent SRS + ICI has varied greatly in the literature, ranging from 2 weeks to 4 months with some studies defining administration within 4 months as concurrent[18,20]; for the purposes of this study, concurrent therapy will be defined as ICI administered within 30 days of SRS. We also hope to explore SRS radionecrosis rates in multi-agent versus single-agent immunotherapy, as well as in melanoma versus non-melanoma brain metastases. Local control will be defined as a less than 20% increase in tumor size following SRS, as previously described using Response Assessment in Neuro-Oncology (RANO) criteria.[27]

2. Objective(s)

2.1. Primary objective

To evaluate toxicity rates of brain metastasis after ICI concurrent with SRS at six months with regard to symptomatic radiation necrosis, defined as a 6-month rate of clinical symptomatology requiring steroid administration (i.e. Decadron), bevacizumab (Avastin), and/or operative intervention concomitant with advanced and routine brain imaging findings consistent with radiation necrosis.

2.2. Secondary objectives

- 6-month local control
- 6-month radiographic radiation necrosis
- 12-month symptomatic radiation necrosis

- 12-month local control
- 12-month radiographic radiation necrosis
- 12-month local control rate by SRS modality
- 12-month local control rate by single versus multi-agent ICI
- 12-month local control rate by melanoma versus non-melanoma brain metastases
- 12-month symptomatic radiation necrosis rate by SRS modality
- 12-month symptomatic radiation necrosis rate by single versus multi-agent ICI
- 12-month symptomatic radiation necrosis rate by melanoma versus non-melanoma brain metastases

3. Outcome Measures

3.1. Primary outcome measure

6-month symptomatic radiation necrosis, defined as a 6-month rate of clinical symptomatology requiring steroid administration (i.e. Decadron) and/or operative intervention concomitant with advanced and routine brain imaging findings consistent with radiation necrosis. Follow-up MRIs will be fused with the planning scan for this assessment.

3.2. Secondary outcome measure

1 6–month local control, defined as a 6-month rate of any new, recurrent or progressing (as defined by RANO criteria) tumor within the planning target volume compared to pre-SRS on any post-treatment MRI by 6 months. Follow-up MRIs will be fused with the planning scan for this assessment.
2 6-month radiographic radiation necrosis, defined as brain imaging findings (MRI, MR Perfusion, MR Spectroscopy, and/or PET) consistent with radiation necrosis.
3 12-month local control
4 12-month symptomatic radiation necrosis
5 12-month radiographic radiation necrosis
6 Evaluation of 12-month local control rate by SRS modality (Gamma Knife versus Linear Accelerator)
7 Evaluation of 12-month local control rate by single agent versus multi-agent ICI
8 Evaluation of 12-month local control rate by melanoma versus non-melanoma brain metastases
9 Evaluation of 12-month symptomatic radiation necrosis rate by SRS modality (Gamma Knife versus Linear Accelerator)
10 Evaluation of 12-month symptomatic radiation necrosis rate by single agent versus multi-agent ICI
11 Evaluation of 12-month symptomatic radiation necrosis rate by melanoma versus non-melanoma brain metastases

4. Eligibility criteria

4.1. Inclusion criteria

1 Brain MRI-confirmed 1–10 solid tumor brain metastases[13]
2 Biopsy-confirmed primary malignancy
3 ds-GPA estimated median survival of at least 6 months[28]
4 Stereotactic radiosurgery candidate per treating Radiation Oncologist
5 ≥ 18 years old at the time of informed consent
6 Ability to provide written informed consent and HIPAA authorization.
7 Absolute lymphocyte count (ALC) > 800/ul[29]
8 Patients currently on cytotoxic chemotherapy are eligible
9 Patients receiving ICI up to 30 days prior to delivery of SRS

Table 1
RADREMI dosing criteria.

Maximum Tumor Diameter	Prescribed Dose
≤ 20 mm	18 Gy
21 – 30 mm	14 Gy
31 – 40 mm	12 Gy

4.2. Exclusion criteria

1 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 follow-up
2 Patients unable to receive MRI Brain
3 Patients with more than 10 brain metastases on MRI Brain
4 Any lesion > 4 cm maximum diameter
5 Total volume of metastatic disease more than 30 cm^3
6 Previous whole brain radiation therapy
7 Previous stereotactic radiosurgery where the 50% isodose line overlaps with current treatment field
8 Already receiving chronic dexamethasone (chronic = ≥ 2 weeks) prior to SRS
9 Not a radiosurgical candidate per Radiation Oncology discretion
10 Existing autoimmune disease
11 Histology not amenable for SRS (i.e. lymphoma)
12 Patients who have an unknown primary

5. Study design

This is a prospective, single arm, pilot study to determine the symptomatic radiation necrosis rate at 6 months utilizing dose-reduced stereotactic radiosurgery with immunotherapy for subjects with a diagnosis of 1–10 brain metastases from MRI and tissue diagnosis of primary malignancy.

6. Study procedures

6.1. Baseline/Screening procedures

The following will be completed prior to radiosurgery:

1 Written informed consent and HIPAA authorization
2 Diagnostic MRI Brain
3 Medical history and clinical examination performed by radiation oncology
4 ALC
5 Baseline ds-GPA, ECOG and KPS

6.2. Stereotactic radiosurgery

Stereotactic radiosurgery will be delivered on all patients utilizing gamma knife or linear accelerator-based techniques as per RADREMI dosing criteria (Table 1) based on tumor diameter. All apparent, previously untreated brain metastases will be treated with radiosurgery at this time.

If any of the following occurs during the MRI Brain planning scan, the subject will be withdrawn from study, not treated on protocol, and replaced:

- The total number of brain metastases sums greater than 10. The subject will be withdrawn and not treated on protocol.
- The total volume of brain metastases is greater than 30 cm3. The subject will be withdrawn and not treated on protocol.

6.3. Follow-Up

Following delivery of stereotactic radiosurgery, all patients will be monitored clinically and with serial MRI Brain scans to determine local control and rate of radiation necrosis. Additional imaging and testing may be performed as deemed necessary by the treating physician.

Initiation/continuation of immunotherapy, chemotherapy and/or other systemic agents will be per medical oncologist discretion.

6.4. One month follow-up

A detailed medical history, toxicity assessment and physical examination including vital signs along with a brain MRI will be performed at 4 weeks after radiosurgery.

6.5. Long term follow up

Subjects will be followed approximately every 3 months (+/- 30 days) after SRS for 1 year. A detailed medical history (including necessity of dexamethasone administration), toxicity assessment and physical examination including vital signs will be performed at each visit. Each follow-up over this time period will also include a Brain MRI with the following sequences: without contrast, with contrast, FLAIR, Diffusion Tensor Imaging (DTI) and Perfusion Weighted Imaging (PWI). The MRI will be analyzed per RANO BM criteria for assessment of local control.[27] The MRI will also be analyzed for radiation necrosis as discussed in Section Eight. Neurologic status will be assessed using the Neurologic Assessment in Neuro-Oncology (NANO) scale (Table 2).[30]

After the 1-year (12-month) follow-up period, subjects will be followed according to their treating physician per standard of care every 3–6 months. MRI Brain scans obtained during this time period may be used for assessment of primary and secondary endpoints; however, they are not mandated to be obtained at particular time intervals. Patients who are unable to travel to Indiana University for follow-up appointments will have records sent to Indiana University at each follow-up (Table 3).

Table 2
Response assessment of target and non-target lesions (Lin et al., 2015).

Target lesions
Complete response
Disappearance of CNS target lesion(s) sustained for at least 4 weeks; with no new lesions, no use of corticosteroids and patient is stable or improved clinically.
Partial response
At least a 30% decrease in the sum longest diameter of CNS target lesion(s), taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
Progressive disease
At least a 20% increase in the sum longest diameter of CNS target lesion(s), taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
Stable disease
Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.
Non-target lesions
Non-target lesions should be assessed qualitatively at each of the time points specified in the protocol.
Complete response
Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
Non-complete response or non-progressive disease
Persistence of one or more non-target CNS lesion or lesions.
Progressive disease
Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

7. Treatment Dose and delivery

The total radiosurgery dose will be specified according to tumor size as noted in Table 1. All patients will be treated to this dose in one session.

FDA-approved stereotactic localization procedures for imaging and treatment delivery will be used. With radiosurgery treatments using the Leksell Gamma Knife Perfexion®, target localization will be performed using the head frame coordinate system. The Leksell GammaPlan® will be used to generate the treatment plan with respect to the coordinate system created by localization. Target volume and isocenter determination will be based on an MRI Brain scan with the patient's head in a stereotactic frame. The imaging study used to deliver the radiosurgical treatment must be the same as used to determine the size of the metastatic lesion(s). Stereotactic MRI slice thickness may not exceed 3 mm. The target volume will include the enhancing portion of the metastatic lesion. Surrounding areas of edema will not be considered part of the target volume.

Linear accelerator based stereotactic localization will be performed using the Encompass® SRS thermoplastic mask immobilization system. The patient will undergo a 1 mm slice thickness helical CT scan that will be fused with the MRI brain T1-weighted post-contrast axial scan used for target delineation. The CT-MRI fusion maximum correlation error must be less than 1.5 mm. The imaging study used to deliver the radiosurgical treatment must be the same as used to determine the size of the metastatic lesion(s). Stereotactic MRI slice thickness may not exceed 3 mm. The target volume will include the enhancing portion of the metastatic lesion. Surrounding areas of edema will not be considered part of the target volume.

The dose will be prescribed to the isodose surface (50–90%), which encompasses the margin of the metastasis, as defined by the imaging studies. The 100% dose will be recorded for each patient.

For patients with multiple brain metastases, stereotactic radiosurgery will be delivered to each lesion that has not previously undergone stereotactic radiosurgery. The prescribed dose will be according to the RADREMI dosing schema as described in Table 1 above. Due to the volumetric summation constraint for the remaining metastases, no single lesion greater than 4 cm will be allowed on study, and, therefore, the above dose prescriptions can be used. If any two lesions are within 0.8–2 cm of each other, the intervening midplane dose will not exceed 13 Gy. This may require treating each respective target with a lesser dose than dictated by the above table. This is designated to minimize toxicity in patients.

(Isodose distributions must be calculated, and the prescription isodose line clearly designated, for each target lesion in all planes.

The dose to the critical structures (Table 4) must meet constraints as designated by TG-101; the small size of the cochlea allows for only a max point dose and not a maximum critical volume above threshold or a threshold dose.[31] If the above constraints cannot be met utilizing the prescribed radiosurgery dose Table 1, then the highest dose to the target volume will be used such that constraints can be met. This will be considered a minor deviation.

Table 3
RADREMI study calendar.

	Baseline Screening Within 30 days of SRS	SRS (stereotactic radiosurgery) Gamma Knife or Linear Accelerator (LINAC)	1 Month Follow Up[a] 30 days post SRS	3 Month Follow Up[a] 90 days post SRS	6 Month Follow Up[a] 180 days post SRS	9 Month Follow Up[a] 270 days post SRS	12 Month Follow Up[b] 1 years post SRS
Radiation Oncology consult and consent	X						
Medical History (including dexamethasone usage)	X		X	X	X	X	X
Physical Examination	X		X	X	X	X	X
Vitals	X	X	X	X	X	X	X
ds-GPA/ECOG performance status/KPS	X		X	X	X	X	X
Diagnostic MRI Brain	X						
MRI Brain Planning Scan[d]		X					
ALC, WBC, Hgb, platelets	X						
Toxicity assessment			X	X	X	X	X
MRI Brain with and without contrast[c]			X	X	X	X	X

[a] Variations of +/- 14 days from the scheduled visit are permitted.
[b] After 12-months post-SRS, subjects will be followed at physician's discretion, approximately every 3-6 months per standard of care. Any MRI Brain, physical exam or vitals obtained at these appointments will be gathered. However, if these procedures are not performed per standard of care, this will not be a deviation.
[c] MRI Brain performed at Indiana University will have sequences including contrast, no contrast, FLAIR, DTI and PWI. If patient receives MRI Brain outside of Indiana University, a minimum of contrast, no contrast and FLAIR will need to be obtained and all sequences mentioned above are encouraged.
[d] Variations of -30 days from the scheduled visit are permitted for linear accelerator based SRS, and may include the baseline screening MRI at the treating radiation oncologist's discretion.

8. Radiation Necrosis

8.1. Radiographic radiation necrosis

Assessment for radiation necrosis will be done based on the contrast-enhanced, FLAIR, Diffusion tensor imaging (DTI) and Perfusion weighted imaging (PWI) MRI sequences. Radiation necrosis is typically a contrast enhancing lesion with surrounding edema noted on contrast-enhanced MRI and FLAIR, respectively; however, it is difficult to distinguish from recurrent tumor. Therefore, DTI and PWI sequences will be analyzed as well. DTI uses fractional anisotropy that reflects the preferential direction of water diffusion along white matter tracks. Fractional anisotropy in radiation necrosis is lower than that for recurrent tumor due to lack of normal axonal fibers or cells within the necrotic area as compared to partially functioning axonal fibers and cells associated with recurrent tumor.[32] PWI assesses intra-lesional and peri-lesional cerebral blood volume. Recurrent tumor is more likely to be associated with higher cerebral blood volume than radiation necrosis as radiation necrosis is devoid of vasculature. The percentage of signal recovery $\geq$ 76.3% has a sensitivity of 96% and specificity of 100% for radiation necrosis as noted on PWI.[33]

8.2. Symptomatic radiation necrosis

Assessment for symptomatic radiation necrosis will be performed based on patients meeting criteria for radiographic radiation necrosis who require steroid administration, bevacizumab, and/or operative resection to treat symptomatic cerebral edema, depending on neurologic severity of symptomatology (patients will be initially managed with standard-of-care Decadron dosing). These will be assessed at each post-SRS follow-up visit in conjunction with Brain MRIs.

9. CRITERIA FOR EVALUATION/REMOVAL FROM STUDY

Every subject should be encouraged to remain in the study. Possible reasons for early withdrawal may include, but are not limited to, the following:

Table 4
Critical structures.

Structure	Maximum critical volume above threshold	Threshold dose (Gy)	Max Point Dose (Gy)
Optic pathway	<0.2 cc	8	10
Brainstem	<0.5 cc	10	15
Cochlea	N/A	N/A	9
Medulla	<1.2 cc	7	

1 Withdrawal of consent – Subject decides to withdraw from the study. This decision must be an "independent decision" that is documented in the source documentation
2 Principal Investigator and/or treating physician discretion – The Principal Investigator and/or treating physician may choose to withdraw a subject from the study if there are safety or other concerns.
3 Subject non-compliance.
4 Subject lost to follow-up.
5 Subject enrolled in hospice care.
6 Subject's death.

10. Statistical Methods

10.1. General considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. If any changes occur, they will be documented in the clinical study report. The statistical analysis methods are outlined below.

10.2. Study design

This is a single-arm pilot study without blinding.

10.3. Analysis datasets

10.3.1. Enrolled population

The enrolled population comprises all subjects who meet the eligibility criteria and are registered onto the study.

10.3.2. Safety population

The safety population comprises all subjects who have received at least one dose of radiation. This set will be used for safety analysis.

10.3.3. Efficacy population

The efficacy population comprises all subjects who have completed stereotactic radiosurgery. This population will be used for efficacy analysis.

10.4. Sample size

An optimum one-stage design is planned. We specify a historical 6-month symptomatic radiation necrosis rate of 16% and an expected 6-month symptomatic radiation necrosis rate of 5%. Then, to achieve a power of 80% and control the type I error below 10%, a total of 40 patients evaluable for symptomatic radiation necrosis will be enrolled in the study. If at most 4 patients will experience symptomatic radiation necrosis in 6 months, the proposed dose reduction is claimed to be desirable. Otherwise, it is undesirable. We assume that at most 5% of the patients will not be evaluable for symptomatic radiation necrosis, which results in a total sample size of 42. In addition, we will add an interim analysis for the 6-month local control rate. When 20 patients have been enrolled in the study with their local control outcome being available, we will conduct a binomial exact test for the null hypothesis that the proposed method can maintain a 6-month local control rate of at least 75%. If p-value of this binomial test is less than 0.05, we will reject the null hypothesis and terminate this study earlier for futility.

10.5. Patient Characteristics and significant protocol violations

Baseline subject characteristics will be tabulated, such as demographics (age, race, gender), and disease characteristics (ds-GPA).

10.6. Analysis of primary objectives

For the primary objective of 6-month symptomatic radiation necrosis for dose-reduced stereotactic radiosurgery concomitant with immunotherapy, the proportion of patients who have symptomatic radiation necrosis at 6 months will be calculated using the Kaplan-Meier method along with a 95% confidence interval. Testing the observed proportion smaller than a baseline 6 month symptomatic radiation necrosis rate of 16% at a type I error rate of 5% using a one-sided binomial exact test will be done.

10.7. Analysis of secondary objectives

For the secondary objectives of 6-month local control, 6-month radiographic radiation necrosis, 12-month symptomatic radiation necrosis, 12-month local control, 12-month radiographic radiation necrosis and 12-month local control rate by SRS modality. Kaplan-Meier methods will be used to provide point estimate with 95% confidence intervals. The method of Klein et al.[34] will be conducted for the group comparison. We acknowledge that due to the sample size, solid conclusions may be difficult to draw for some of these objectives due to the high heterogeneity of different populations (melanoma versus lung versus breast cancer metastases). We also acknowledge the possibilities of the maximum rate of symptomatic radiation necrosis being better reflected by the 12-month rate than the 6-month rate, or of symptomatic radiation necrosis rate being affected by the tri-fractionated scheme available with the most recent evolution of Gamma Knife devices.

11. Discussion

This study is the first prospective trial to investigate the safety of dose-reduced SRS in treatment of brain metastases with concomitant ICI (administered before SRS). The findings from our primary and secondary endpoints should provide fertile soil for future multi-institutional collaborative efficacy trials of RADREMI dosing for this patient population, potentially ushering in a new era of reduced toxicity in the optimal management of this increasing patient population.

Conflict of interest

None.

Financial disclosure

None.

Statement of author contributions

Conception and design: McClelland, Lautenschlaeger, Zang, Watson

Manuscript writing: McClelland, Zang, Shiue, Agrawal, Rhome, Watson

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References

1. Nabors LB, Portnow J, Ammirati M, et al. NCCN guidelines insights: Central nervous system cancers, version 1.2017. *J Natl Compr Canc Netw*. 2017;15(11):1331–1345.
2. Pruitt AA. Epidemiology, treatment, and complications of central nervous system metastases. *Continuum (Minneap Minn)*. 2017;23(6,Neuro-oncology):1580–1600.
3. Gibney GT, Forsyth PA, Sondak VK. Melanoma in the brain: Biology and therapeutic options. *Melanoma Res*. 2012;22(3):177–183.
4. Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol*. 2004;22(7):1293–1300.
5. Davies MA, Liu P, McIntyre S, et al. Prognostic factors for survival in melanoma patients with brain metastases. *Cancer*. 2011;117(8):1687–1696.
6. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379(8):722–730.
7. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: An open-label, phase 2 trial. *Lancet Oncol*. 2012;13(5):459–465.
8. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: Early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(7):976–983.
9. Di Giacomo AM, Ascierto PA, Pilla L, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): An open-label, single-arm phase 2 trial. *Lancet Oncol*. 2012;13(9):879–886.
10. Bernard ME, Wegner RE, Reineman K, et al. Linear accelerator based stereotactic radiosurgery for melanoma brain metastases. *J Cancer Res Ther*. 2012;8(2):215–221.
11. Minniti G, Paolini S, D'Andrea G, et al. Outcomes of postoperative stereotactic radiosurgery to the resection cavity versus stereotactic radiosurgery alone for melanoma brain metastases. *J Neurooncol*. 2017;132(3):455–462.
12. Matsunaga S, Shuto T, Yamamoto M, et al. Gamma knife radiosurgery for metastatic brain tumors from malignant melanomas: A japanese multi-

institutional cooperative and retrospective cohort study (JLGK1501). *Stereotact Funct Neurosurg*. 2018;96(3):162–171.
13. Yamamoto M, Higuchi Y, Sato Y, Aiyama H, Kasuya H, Barfod BE. Stereotactic radiosurgery for patients with 10 or more brain metastases. *Prog Neurol Surg*. 2019;34:110–124.
14. Kotecha R, Kim JM, Miller JA, et al. The impact of sequencing PD-1/PD-L1 inhibitors and stereotactic radiosurgery for patients with brain metastasis. *Neuro Oncol*. 2019, pii: noz046. doi: 10.1093/neuonc/noz046. [Epub ahead of print].
15. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. *JAMA Oncol*. 2018;4(8):1123–1124.
16. Cohen-Inbar O, Shih HH, Xu Z, Schlesinger D, Sheehan JP. The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab. *J Neurosurg*. 2017;127(5):1007–1014.
17. Williams NL, Wuthrick EJ, Kim H, et al. Phase 1 study of ipilimumab combined with whole brain radiation therapy or radiosurgery for melanoma patients with brain metastases. *Int J Radiat Oncol Biol Phys*. 2017;99(1):22–30.
18. Anderson ES, Postow MA, Wolchok JD, et al. Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment. *J Immunother Cancer*. 2017;5(1):76.
19. Yusuf MB, Amsbaugh MJ, Burton E, Chesney J, Woo S. Peri-SRS administration of immune checkpoint therapy for melanoma metastatic to the brain: Investigating efficacy and the effects of relative treatment timing on lesion response. *World Neurosurg*. 2017;100, 632-640.e4.
20. Chen L, Douglass J, Kleinberg L, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung Cancer, melanoma, and renal cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;100(4):916–925.
21. Skrepnik T, Sundararajan S, Cui H, Stea B. Improved time to disease progression in the brain in patients with melanoma brain metastases treated with concurrent delivery of radiosurgery and ipilimumab. *Oncoimmunology*. 2017;6(3):e1283461.
22. Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. *Radiother Oncol*. 2019;130:104–112.
23. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. 2000;47(2):291–298.
24. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): A multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1049–1060.
25. Shehata MK, Young B, Reid B, et al. Stereotatic radiosurgery of 468 brain metastases < or =2 cm: Implications for SRS dose and whole brain radiation therapy. *Int J Radiat Oncol Biol Phys*. 2004;59(1):87–93.
26. Colaco RJ, Yu JB, Bond JS, et al. A contemporary dose selection algorithm for stereotactic radiosurgery in the treatment of brain metastases - an initial report. *J Radiosurg SBRT*. 2016;4(1):43–52.
27. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: Proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270–8.
28. Woody NM, Greer MD, Reddy CA, et al. Validation of the disease-specific GPA for patients with 1 to 3 synchronous brain metastases in newly diagnosed NSCLC. *Clin Lung Cancer*. 2018;19(1):e141–e147.
29. Ku GY, Yuan J, Page DB, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: Lymphocyte count after 2 doses correlates with survival. *Cancer*. 2010;116(7):1767–1775.
30. Nayak L, DeAngelis LM, Brandes AA, et al. The Neurologic Assessment in Neuro-Oncology (NANO) scale: A tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. *Neuro Oncol*. 2017;19(5):625–635.
31. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. *Med Phys*. 2010;37(8):4078–4101. Erratum in: Med Phys. 2012 Jan;39(1):563. Dosage error in article text.
32. Shah R, Vattoth S, Jacob R, et al. Radiation necrosis in the brain: Imaging features and differentiation from tumor recurrence. *Radiographics*. 2012;32(5):1343–1359.
33. Barajas RF, Chang JS, Sneed PK, Segal MR, McDermott MW, Cha S. Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *AJNR Am J Neuroradiol*. 2009;30(2):367–372.
34. Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. *Stat Med*. 2007;26(24):4505–4519.