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The effect of surgery on radiation necrosis in irradiated brain metastases: extent of resection and long-term clinical and radiographic outcomes

William C. Newman, M.D.[1], **Jacob Goldberg, M.D.**[2,3], **Sergio W. Guadix, B.A.**[2,3], **Samantha Brown**[4], **Anne S. Reiner, M.P.H.**[4], **Katherine Panageas, M.D.**[4], **Kathryn Beal, M.D.**[5], **Cameron W. Brennan, M.D.**[2], **Viviane Tabar, M.D.**[2], **Robert J. Young, M.D.**[6], **Nelson S. Moss, M.D.**[2]

[1]Department of Neurosurgery, Louisiana State University Health Sciences, Shreveport, LA, USA

[2]Department of Neurological Surgery and Brain Metastasis Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[3]Department of Neurological Surgery, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, NY, USA

[4]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[5]Department of Radiation Oncology and Brain Metastasis Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[6]Department of Radiology and Brain Metastasis Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

Objective—Radiation therapy is a cornerstone of brain metastasis (BrM) management but carries the risk of radiation necrosis (RN), which can require resection for palliation or diagnosis.

*Corresponding Author: Nelson S. Moss, MD, Department of Neurosurgery and Brain Metastasis Center, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Telephone: 212-639-7075, mossn@mskcc.org.

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We sought to determine the relationship between extent of resection (EOR) of pathologically-confirmed RN and postoperative radiographic and symptomatic outcomes.

Methods—A single-center retrospective review was performed at an NCI-designated Comprehensive Cancer Center to identify all surgically-resected, previously-irradiated necrotic BrM without admixed recurrent malignancy from 2003-2018. Clinical, pathologic and radiographic parameters were collected. Volumetric analysis determined EOR and longitudinally evaluated perilesional T2-FLAIR signal preoperatively, postoperatively, and at 3-, 6-, 12-, and 24-months postoperatively when available. Rates of time to 50% T2-FLAIR reduction was calculated using cumulative incidence in the competing risks setting with last follow-up and death as competing events. The Spearman method was used to calculate correlation coefficients, and continuous variables for T2-FLAIR signal change, including EOR, were compared across groups.

Results—Forty-six patients were included. Most underwent prior stereotactic radiosurgery with or without whole-brain irradiation (n=42, 91%). Twenty-seven operations resulted in gross-total resection (59%; GTR). For the full cohort, T2-FLAIR edema decreased by a mean of 78% by 6 months postoperatively that was durable to last follow-up ($p<0.05$). EOR correlated with edema reduction at last follow-up, with significantly greater T2-FLAIR reduction with GTR versus subtotal resection ($p<0.05$). Among surviving patients, a significant proportion were able to decrease their steroid use: steroid-dependency decreased from 54% preoperatively to 15% at 12 months postoperatively ($p=0.001$).

Conclusions—RN resection conferred both durable T2-FLAIR reduction, which correlated with EOR; and reduced steroid dependency.

Keywords

Brain metastasis; radiation necrosis; radiation therapy; surgical resection

Introduction

Radiation therapy (RT) is a cornerstone of brain metastasis (BrM) treatment, with or without surgical resection or CNS-active systemic therapy. However, radiation necrosis (RN) is a common complication of intracranial radiation characterized by cerebral inflammation and perilesional edema, occurring in some 5-40% of treated lesions.[1,23-8] RN incidence is dependent on radiation dose, tumor size, and in some cases adjuvant treatments (e.g. immune checkpoint inhibition), and is challenging to quantify due to inconsistent radiographic appearance and varying diagnostic criteria, with some definitions including only the symptomatic proportion. Furthermore, histopathological confirmation is rarely available and admixed recurrent tumor often confounds the radiographic picture, making study of these lesions difficult.[9] Initial management is conservative with observation for asymptomatic lesions or, for symptomatic lesions, oral corticosteroids, VEGF inhibitor bevacizumab, oral pentoxifylline and vitamin E, laser interstitial thermal therapy (LITT), or hyperbaric oxygen.[10-19] Once palliative conservative measures have failed, surgical resection is considered. Additionally, in the setting of noninvasive diagnostic uncertainty using standard magnetic resonance imaging (MRI), perfusion mapping, positron emission

tomography (PET) scans and other imaging modalities, surgical resection also serves to provide tissue diagnosis when clinically warranted.

Palliative RN resection results in reduced perilesional edema and patient symptoms.[8,22-26] However, the role of extent of resection (EOR) on edema reduction and symptomatic control and durability have not been established, which is a significant knowledge gap given that complete removal of necrotic, previously-irradiated tumors can be precluded based on eloquent location. Furthermore, the margins of a necrotic tumor can be difficult to define intraoperatively as compared to generally encapsulated untreated BrM and hypercellular gliomas, for example, and the unclear clinical significance of surgical aggressiveness towards this goal can obscure surgical decision-making. Therefore, we retrospectively reviewed a large NCI-designated Comprehensive Cancer Center experience of resected, pathologically-confirmed RN free of admixed viable metastatic disease and tracked long-term radiographic and symptomatic changes with volumetrically-ascertained EOR to inform the relevant relationships.

Methods

Design

This is a retrospective, single-center observational study. The institutional review board approved this study (IRB#16-1531) and granted a waiver of consent.

Patient Selection

Consecutive patients who underwent open surgical resection of previously-irradiated BrMs between 2003-2018 were screened, generating 312 cases. Of these, 241 were excluded for pathologic diagnosis of viable tumor admixed with RN as determined by a neuropathologist. Cases were excluded if there was any identifiable viable metastatic disease given the indeterminate clinical significance of these deposits. Of the 71 remaining specimens with pure RN, 20 were excluded due to imaging follow-up of <1 year given the *a priori* hypothesis that surgical effects would be durable to that timepoint; purely cystic lesion on imaging; or pathologic description of a predominantly-hemorrhagic lesion confounding the area of pathologically pure RN. At our institution, patients with suspected RN are treated conservatively with close radiographic surveillance when asymptomatic, and medically when symptomatic. Resection is generally offered with palliative intent in the setting of refractory symptoms (e.g. steroid dependency/toxicity or bevacizumab intolerance/contraindication including thromboembolism or hemorrhage history), or when pathologic confirmation is indicated (e.g. in the setting of suspected recurrence or infection). Three patients underwent same-site reoperation for recurrent RN, and two patients each underwent additional distant-site necrosis resections; only these patients' first surgeries were included for analysis. This resulted in a study population of 46 distinct patients with 1 resected necrotic lesion each.

Pathologic Criteria for Radiation Necrosis

RN was independently diagnosed by the institution's neuropathologists, and was defined by the presence of coagulative and fibrinoid necrosis, hyalinized vasculature, focal areas of

perivascular lymphocytes, and associated inflammation.[27] Multiple sites from the specimens were examined as per institutional protocol to evaluate for any viable recurrent metastatic disease, which was grounds for exclusion from this study.

Surgical Treatment and Follow-up

Included patients had immediate pre- and post-operative (within 48 hours) contrasted magnetic resonance imaging per institutional practice. Postoperative MR imaging at 3-, 6-, 12-, and 24-months were also reviewed where available; not all patients had imaging at each timepoint. Patients who did not have ≥12 months follow-up were excluded given the *a priori* hypothesis above to ensure appropriate classification of patients with transient versus durable symptomatic changes. The contrast-enhancing volume was contoured on the preoperative and immediately post-operative 3D T1 pre- and post-contrast images using the Brainlab SmartBrush segmentation tool (Munich, Germany) to determine EOR. Gross total resection (GTR) was defined as 100% removal of the enhancing tumor and as subtotal resection (STR) as <100% (i.e. including near-total resections). T2-FLAIR signal was also segmented using the SmartBrush tool. Symptoms, steroid use, and antiepileptic use were obtained at each of these timepoints when available. Symptoms were extracted from the inpatient and outpatient visit notes, which included review of systems and narrative descriptions. More detailed descriptors such as Karnofsky Performance Scale and Eastern Cooperative Oncology Group performance status were not consistently available and were therefore not included. In the immediate postoperative period, patients typically received an increased steroid dose that was then weaned as tolerated by symptoms and irrespective of EOR.

Statistical Analysis

The study population was characterized using descriptive statistics, including frequencies, medians, and interquartile ranges. Overall survival (OS) was calculated from date of surgery to death or last follow-up and presented using Kaplan-Meier curves. Rates of time to 50% T2-FLAIR signal reduction were calculated using cumulative incidence in the competing risks setting, where follow-up time was calculated from date of surgery to MRI date where 50% T2-FLAIR signal reduction was achieved, death, or last follow-up, whichever occurred first. The Spearman method was used to calculate correlation coefficients. Continuous variables for T2-FLAIR signal percentage change were compared across groups using the Wilcoxon rank sum test and Kruskal-Wallis test where appropriate. McNemar's test was used to assess the difference in proportions of patients using steroids. The Wilcoxon signed rank test was performed to assess steroid use reduction over time. Fisher's exact test was used to evaluate the association between EOR and postoperative symptom changes. All tests were two-sided with a statistical significance level of <0.05. All analyses were performed using R statistical software.

Results

Descriptive Characteristics

Forty-six unique patients were included (Table 1). Three patients ultimately underwent same-site reoperation for recurrent RN, and 2 underwent RN resection at a different

intracranial site. Only unique patients at the time of their first surgery were included in the analysis. Median age at surgery was 60 years (range 35-83). Lesions were most commonly parietal (N=14, 30%), frontal (N=13, 28%) and occipital (N=8, 17%). Twelve had a prior craniotomy plus adjuvant or neoadjuvant index-site irradiation (26%). Histologies included non-small cell lung cancer, (N=20, 43%) breast cancer (N=9, 20%) and melanoma (N=9 each, 19%), in line with the incidence of brain metastases. The most common dominant referable symptoms were headache (N=13, 27%) and seizures (N=11, 23%). Twenty-five patients (54%) required corticosteroids immediately preoperatively (additional patients had been previously treated with steroid courses) and 4 (8%) had received bevacizumab at any point for RN. Preoperatively, patients were generally followed with serial MRI, perfusion sequences and/or FDG-PET in cases of diagnostic uncertainty; all resections were performed with palliative intent. Twenty-seven lesions underwent GTR (59%) and the remainder STR. The EOR interquartile range (IQR) was 80-100%. Mean time between preoperative MRI and surgery was 5.8 days. Median radiographic follow-up length was 22 months; 72% had a 24-month scan.

Radiation History

All lesions had been previously irradiated. Thirty-six patients (78%) had undergone stereotactic radiosurgery (SRS) prior to RN development (n=25 single-fraction, 11 hypofractionated), 6 (13%) received a combination of SRS plus whole-brain radiation therapy (WBRT), and 4 (9%) WBRT alone. The median time from most recent radiation treatment to RN surgical resection was 11 months (IQR 6-19).

Postoperative Changes in T2-FLAIR Signal Volume

Among all resected lesions, there was a statistically significant mean T2-FLAIR signal decrease versus baseline preoperative volume of 63% at 3 months, 78% at 6 months, 78% at 12 months, and 80% at last follow-up up to 24 months ($p<0.05$ for all) (Figure 1). GTR resulted in a significantly greater T2-FLAIR reduction versus STR by last follow-up ($p<0.05$). Patients with GTR experienced more rapid cumulative incidence of 50% T2-FLAIR volume reduction compared versus those with STR ($p=0.05$) (Figure 1B).

There was no significant correlation between the ratio of preoperative contrast-enhancing tumor volume-to-T2-FLAIR volume with postoperative T2-FLAIR volume reduction on an absolute basis, however T2-FLAIR reduction was proportional to preoperative T2-FLAIR volume. Similarly, while preoperative contrast-enhancing tumor volume was not associated with T2-FLAIR volume reduction, T2-FLAIR reduction was proportional to preoperative enhancing RN volume. Figure 2 demonstrates representative T2-FLAIR changes in with STR and GTR. Exploratory analyses identified no differences in time to 50% T2-FLAIR reduction by histology (non-small cell lung cancer vs. other), brain location (parietal lobe vs. other), or form of preoperative radiation (single-fraction vs. hypofractionated SRS; Gray's test p-values 0.37-0.91).

Postoperative Symptom Changes and Steroid Use

Of the 42 patients with symptom data recorded, 23 (55%) experienced symptomatic improvement at 3 months postoperatively that remained stable thereafter, and 15 (36%)

had stable symptoms postoperatively (Table 2). The remaining 4 (9%) experienced worsened symptoms. Of these, 1 with headaches suffered progressive ICP-related symptoms owing to multiple progressive lesions, another suffered from increased seizure frequency requiring anticonvulsant titration, another suffered from worsening sensory symptoms following resection from primary sensory cortex, and the fourth suffered from progressive neurologic decline referable to the subtotally-resected index necrotic occipital necrotic metastasis with progressive edema and other progressive lesions. There was no statistically-significant association between EOR and postoperative symptom changes or difference in symptom reduction when stratifying by focal deficits versus ICP-related symptoms ($p>0.05$). There was no statistically-significant correlation between T2-FLAIR volume percent change and postoperative symptom improvement at any timepoint ($p>0.05$). Across the cohort, the proportion of patients not requiring steroids among those who survived at least 12 months (N=39) increased from 18/39 preoperatively (46%) to 33/39 (85%) at 12 months ($p=0.001$). Among those patients remaining on steroids, their use decreased from 8mg daily dexamethasone equivalents preoperatively (range 2-36) to 3mg at 12-months postoperatively (range 1-8, $p=0.063$).

Patient Survival and Follow-up

Median radiographic follow-up was 22 months (Table 1). Median OS was 86 months, with no significant difference in OS among those undergoing GTR versus STR ($p=0.46$, Figure 1). Among those with known cause of death, 9 were CNS-related deaths and 7 deaths non-CNS related.

Patients Requiring Repeat Same-Site RN Resection

Of the 3 patients undergoing repeat surgery for recurrent RN, 2 were melanoma metastases and 1 non-small cell lung cancer.All 3 suffered from seizures as their dominant referable complaint. One had initially undergone GTR with subsequent partial resection of the recurrent necrotic (again pathologically confirmed to harbor no viable tumor), with 53% reduction in T2-FLAIR at final follow-up. The other 2 underwent 79% and 96% EOR at the first RN operation with GTR of the recurrent lesion, with pathology also confirming persistent metastasis-free necrosis. Those patients experienced 47% and 73% reductions in T2-FLAIR by last follow-up, respectively. There was no difference in preoperative contrast-enhancing volume or ratio of T2-FLAIR to enhancement among these cases as compared to the remainder of the cohort studied.

Postoperative Complications

No patients experienced new post-operative deficits that were persistent at 3-month follow-up, death from surgical complications, wound complications requiring operative intervention, or other surgical-site infections. One patient did suffer from worsening of preexisting sensory symptoms following a postcentral gyrus metastasis resection.

Discussion

This series represents the largest and longest-followed reported cohort of surgically-removed and pathologically-confirmed RN, and the first analysis of EOR on long-term outcome of

this condition (Table 3).[8,22,24,28] Additionally, this cohort only includes patients with brain metastases, a population which unlike gliomas harbors discrete tumors without admixed or infiltrative neoplastic disease confounding outcome study, and additionally provides important information on outcomes with subtotal resection. Our findings are in line with those of case reports and heterogeneous retrospective studies which demonstrate that resection of the contrast-enhancing RN leads to radiographic and symptomatic improvement with low morbidity.[8,22,24]

When our study is combined with the existing literature, a clearer picture of the role of surgical resection of refractory, symptomatic RN arises. Several small series have shown that RN resection is safe and provides symptomatic relief.[8,22,24,28] Shah et al. further detailed the positive impact of surgical resection on Karnofsky Performance Score in BrM patients with symptomatic RN with limited follow-up of 13 months.[22] McPherson et al.[28] and Shah et al.[22] both demonstrated the role of resection in reducing postoperative steroid dependency. Our data support these findings, and also add several key insights into the effects of surgical resection on necrotic irradiated BrM which inform surgical candidacy and prognosis.

First, our data demonstrate that the majority of the T2-FLAIR reduction surrounding RN occurs by 6 months and is durable thereafter, which is important for the growing population of patients with brain metastases requiring irradiation, with inherently limited if growing life expectancy[29]. To this point, we identify a median survival of 86 months in this cohort which is substantially longer than the at-large BrM population and those described in other large surgical BrM series (Figure 1D).[30] Acknowledging surgical selection bias for patients who survived long enough to develop RN and who had follow-up of ≥1 year, this finding likely reflects a population with treatable, well-controlled CNS and primary/extracranial disease and highlights the value of such palliative and diagnostic treatments for this patient group, even those with presumed RN; indeed some half of patients who died in this cohort suffered non-CNS cause of death. In the modern era of aggressive local brain-directed therapies for patients with CNS-centric metastatic disease, a growing body of literature suggests both increasing survival and, in some cases, an increasing proportion of non-neurologic death, making control of brain metastases and their complications ever more important.[29,31]

Importantly, we show that EOR is indeed related to radiographic outcome of volumetric T2-FLAIR signal, a critical finding not previously documented in the literature and which may guide clinical practice. In those patients in whom GTR was achieved, a significantly larger reduction in T2-FLAIR volume was seen by last follow-up compared to those who underwent STR. Additionally, time to 50% reduction in T2-FLAIR volume was accomplished more quickly in patients with GTR than in those with STR. The importance of this finding is underlined by our GTR rate of just 59%, which we posit is related to (1) infiltrative margins that are more microsurgically difficult to distinguish from normal brain than encapsulated viable metastases, (2) eloquent tract involvement/abutment in some cases, and (3) surgeon hesitancy to pursue aggressive removal in the face of intraoperative assessments of necrosis (including gross appearance and frozen section readouts) and a lack of prior EOR data in this space.

While alternative non-invasive, and minimally-invasive strategies including LITT have some evidence of efficacy, these also carry associated toxicity profiles. Furthermore, LITT is typically reserved for smaller necrotic lesions (on the order of 2.2cc described in a recent series) than those described in this series of symptomatic tumors given the potential for short-term swelling with the former approach, and long-term data have yet to mature.[17]

Steroid use was significantly reduced at all evaluated time points, which is a meaningful clinical endpoint for patients with metastatic disease including patients who may require immunotherapy or cell-based therapeutics for extracranial disease control. Multiple studies have suggested that steroid use blunts the CNS- and systemic effects of immunotherapies including checkpoint inhibitors, which are a mainstay in several cancers including melanoma. Thus, rapid steroid reduction is increasingly important.[29,32-35] We did not identify a statistically meaningful correlation between EOR and symptom amelioration, which we hypothesize may be related to a combination of partial masking by steroid use (which was indeed reduced with surgical treatment), underpowering due to the small number of patients who met inclusion criteria, heterogeneity of referable symptoms, and the rarity of this indication for RN resection. Due to the significant association of EOR with reduction in T2-FLAIR volume, we believe it is reasonable to infer that symptomatic improvement would follow a similar pattern if the patient population were larger or more homogeneous. For patients with symptomatic RN, the significant EOR association with FLAIR reduction can be used as a potential surrogate to guide surgical decision-making. However, the comparable symptomatic relief seen in both groups also supports the conclusion that subtotal resection of the contrast enhancing lesion is a reasonable palliative approach when complete removal is not feasible.

It is important to note that while surgical resection of RN yielded significant and durable radiographic and symptomatic improvements, there were cases with refractory RN requiring repeat intervention, which were all re-proven histologically to represent pure RN without evidence of admixed viable metastatic disease. The only point of commonality between in these 3 patients was a preoperative contrast-enhancing lesion volume <7cc with T2-FLAIR volume ≥6 times that of the enhancing lesion volume. There were no other common factors with respect to tumor histology, location, or type of pre-operative RT. None received additional postoperative RT. These cases highlight that further basic investigation to understand the physiology of RN including clinico-pathologic correlatives (histology, location, prior radiation type), and outlier analysis of medically- and surgically-refractory cases, are both warranted and underway.

Though our study is the largest analysis of the relationship of EOR on RN resection outcomes, there are several important limitations. First, our study is retrospective and thus subject to selection bias and incomplete data. We attempted to limit the impact of the former by utilizing cross-sectional databases to identify patients who met inclusion criteria. Retrospective and subjective symptomatology documentation convey a degree of heterogeneity to the data. As a result, while we confirmed previous findings of symptomatic improvement with RN resection, we were not able to establish a statistically meaningful correlation between EOR and these improvements which we hypothesize is due limited powering. Third, while the pathologists independently evaluated multiple areas of each

specimen prior to determining that there was no evidence of viable tumor, given the importance of this distinction to patients' subsequent care, these findings are limited by the potential of sampling error which may partially explain the difference seen in the non-GTR vs GTR groups. However, this is not thought to play a significant role given that durable responses were seen in all but 3 cases, which included both GTR and non-GTR cases; each tumor had several cubic centimeters of resected tissue specimen available to the neuropathologists as these were open resections, and institutional protocol for such cases includes multifocal sampling given the importance of accurate diagnosis in these cases; and long survival was identified in both cohorts relative to the brain-metastatic population consistent with well-controlled disease, together adding to the confidence that all cases indeed represented pure RN. Fourth, our study represents the experience of a single center and may not reflect the surgical and cancer-directed outcomes experienced elsewhere. Prospective and multi-center investigations are needed both into RN treatment and risk factors (tumor-intrinsic and -extrinsic). Finally, the separate-but-related clinical entity of post-irradiation RN plus admixed recurrent malignancy is also worthy of future attention.

Nonetheless, our data showing consistent, durable efficacy of surgical resection of pathologically-confirmed radiation necrosis over a 15-year study period, in a range of brain metastasis diagnoses, make these findings broadly generalizable, and identify the key role of resection in conveying palliative benefit to this growing population.

Conclusions

Surgical resection of RN conferred durable radiographic improvement, and reduced steroid dependency, with EOR correlating with durable radiographic improvement. GTR conferred better improvements in perilesional edema versus STR.

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Abbreviations:

BrM	Brain Metastasis
EOR	Extent of Resection
GTR	Gross Total Resection
LITT	Laser Interstitial Thermal Therapy
RN	Radiation Necrosis
RT	Radiation Therapy
SRS	Stereotactic Radiosurgery
STR	Subtotal Resection
WBRT	Whole Brain Radiation Therapy

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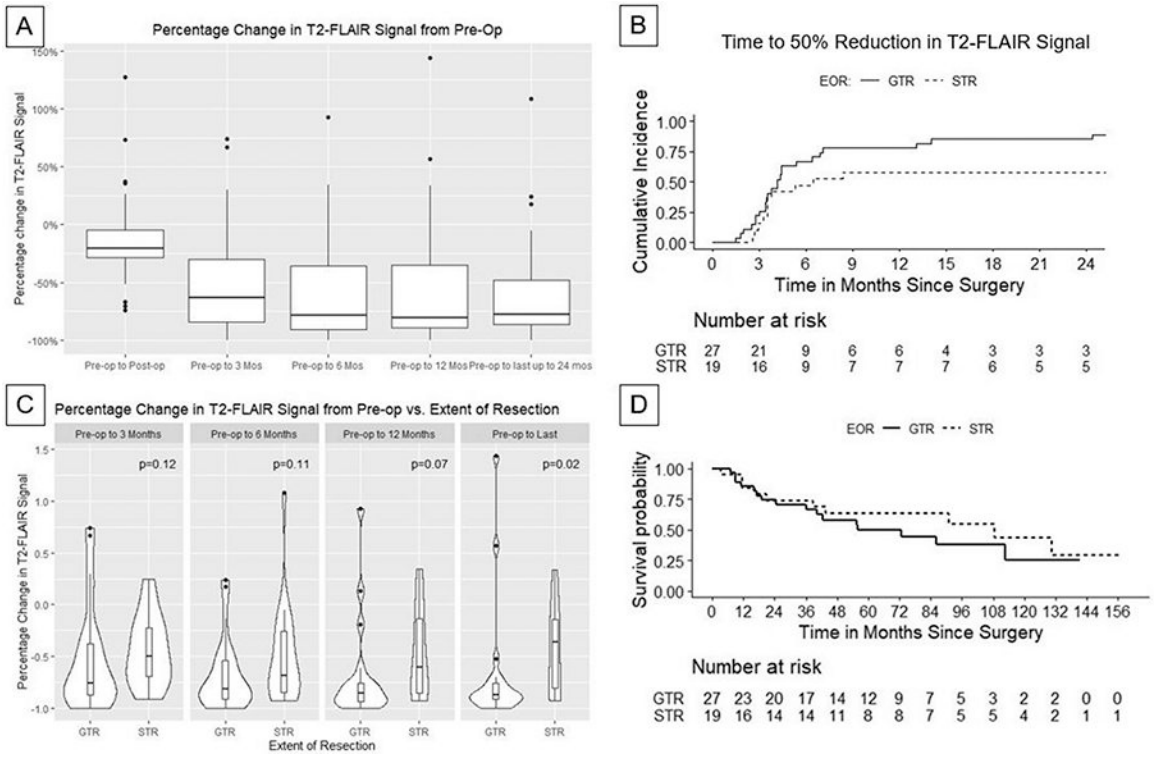

Figure 1:

A) Percent change in T2-FLAIR signal over time relative to pre-operative T2-FLAIR volume. B) Kaplan-Meier curves demonstrating observed reduction in T2-FLAIR signal stratified by extent of resection (EOR). C) Percent change in T2-FLAIR signal over time as a function of extent of resection (gross-total vs. subtotal resection). D) Kaplan-Meier curves for overall survival for patients with gross total resection (GTR) and subtotal resection (STR).

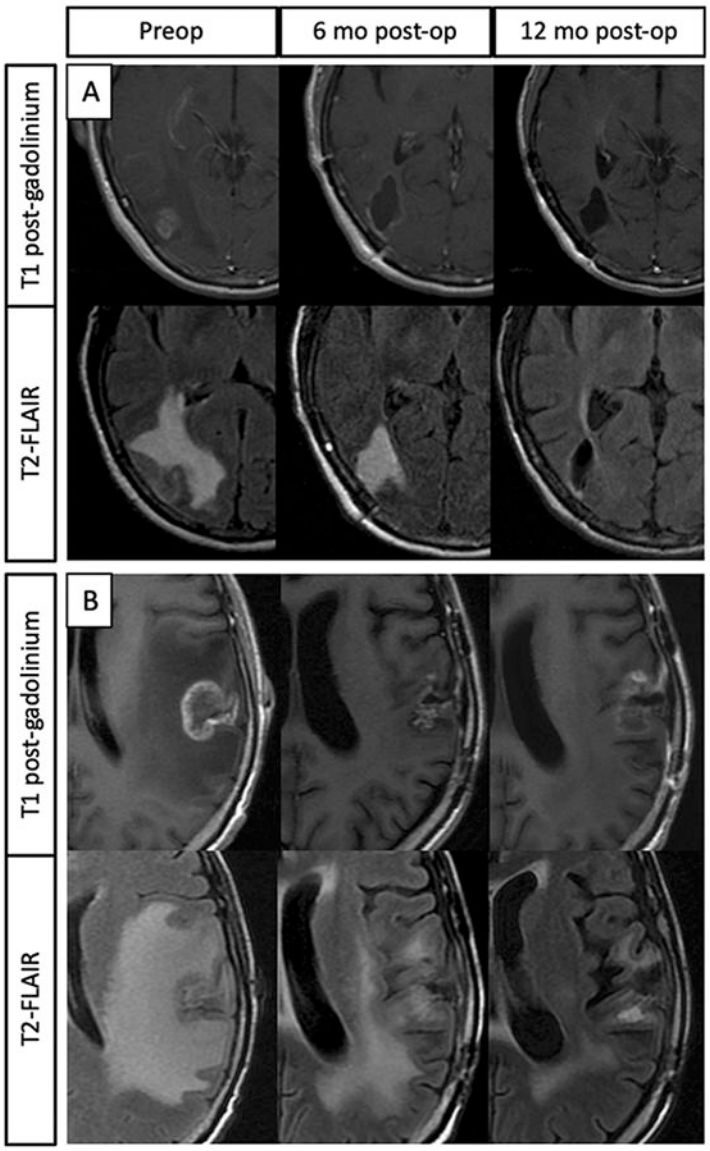

Figure 2:

A) Representative images of a gross-totally resected RN lesion. The T1 post-contrast sequences demonstrate gross total resection of enhancing lesional tissue. The T2-FLAIR sequences demonstrate significant preoperative perilesional signal which progressively decreases post-operatively. B) Representative images of a sub-totally resected RN lesion. T1 post contrast images demonstrate a small amount of residual contrast enhancement at the 6- and 12-month post-operative time points. The T2-FLAIR sequences reveal significant perilesional signal preoperatively, which progressively decreases post-operatively.

Table 1:

Patient characteristics.

Variable	N = 46 (%)
Gender	
Female	26 (57%)
Male	20 (43%)
Age at Surgery	60 (35, 83)
Preoperative Radiation Therapy	
SRS – hypofractionated	11 (24%)
SRS – single-fraction	25 (54%)
WBRT	4 (9%)
WBRT + SRS	6 (13%)
Surgical Lobe	
Parietal	14 (30%)
Frontal	13 (28%)
Occipital	8 (18%)
Cerebellum	5 (11%)
Temporal	5 (11%)
Insula	1 (2%)
Laterality	
Left	21 (46%)
Right	25 (54%)
Prior Craniotomy at Index Site	
No	34 (74%)
Yes	12 (26%)
Pathologic Diagnosis	
NSCLC	20 (44%)
Breast Cancer	9 (20%)
Melanoma	8 (17%)
Small Cell Lung Cancer	4 (9%)
Renal Cell Carcinoma	2 (4%)
Sarcoma	1 (2%)
Testicular Cancer	1 (2%)
Thyroid Cancer	1 (2%)
Dominant Preoperative Symptom	
Gait Disturbance	2 (4%)
Headache	13 (28%)
Seizure	11 (24%)
Sensory Disturbance	1 (2%)
Speech Disturbance	2 (4%)

Variable	**N = 46 (%)**
Vision Disturbance	2 (4%)
Weakness	3 (7%)
Other	9 (20%)
Unknown	3 (7%)
Extent of Resection	
Gross Total Resection	27 (59%)
Subtotal Resection	19 (41%)
Percent Resection	100 (33, 100)

Statistics presented: N (%); median (minimum, maximum)

*NSCLC = Non-small Cell Lung Cancer, SRS = Stereotactic Radiosurgery, WBRT = Whole Brain Radiation Therapy

Table 2.

Change in patient symptoms by 3 months postoperatively; and steroid dependency

Change in dominant RN-referable symptom					
Change in symptom	**Total, N=46**	**GTR, N=27**	**STR, N=19**	**Focal deficits, N=33**	**ICP-related symptoms, N=13**
Improved	23 (50%)	14 (52%)	9 (47%)	15 (46%)	8 (61%)
Unchanged	15 (32%)	10 (37%)	5 (26%)	11 (33%)	4 (31%)
Worsened	4 (9%)	2 (7%)	2 (11%)	3 (9%)	1 (8%)
Unknown	4 (9%)	1 (4%)	3 (16%)	4 (12%)	0 (0%)
Steroid dependency					
Time point (N)	**Patients alive not taking steroids, N (%)**				
Preoperative	21/46 (46%)				
3 months postoperatively	35/46 (76%)				
6 months postoperatively	41/45 (91%)				
12 months postoperatively	33/39 (85%) *				

* p=0.001 versus preoperatively in patients alive at both timepoints.

Table 3:

Literature review on the surgical management of brain metastasis radiation necrosis

Authors (year)	Diagnoses included	Treatment	Preoperative tumor volume	Pathologic confirmation of RN	Extent of resection	Follow up duration	Outcomes	Periprocedural complications
Kimura T, et al. (2003)	Brain metastases	Resection (N=4), medical therapy (steroids, heparin, warfarin; N=2)	Not reported	Yes (surgical cases only)	3/4 GTR (75%); 1/4 STR (25%)	Not specified	2/4 surgical patients with qualitative improvement; 2/4 with subsequent worsening. Both medically managed patients with progressive neurologic decline.	Not specified
Mcpherson CM et al (2004)	Brain metastases (N=3) plus anaplastic astrocytoma, anaplastic oligodendroglioma and glioblastoma (N=8)	Resection (N=11)	Not reported	No	9/11 GTR (82%); 2/11 STR (18%)	13 months (mean; range 3-26)	Significant reduction in steroid use in 9/9 steroid-dependent patients; 8/11 patients with subjectively stable to improved neurologic function; 3/11 with worsened or new referable symptoms	Wound infection, carotid dissection, pulmonary embolism (N=1 each)
Telera S, et al. (2013)	Brain metastases	Resection (N=15)	Not reported	No: mixed group of pure RN (N=7), admixed RN+viable tumor (N=8)	15/15 GTR (100%)	14 months (median; range 6-38)	Post hospitalization outcomes not reported; brain edema resolved in all cases by 4 weeks, allowing “substantial” reduction or suspension of corticosteroid therapy	Transient dysphasia (N=2); seizure, CSF fistula, cerebellar ataxia, extremity weakness (N=1 each)
Shah AH, et al. (2020)	Brain metastases (N=14), high-grade glioma (6), meningioma (3), esthesioneuroblastoma (1)	Resection (N=24)	Not reported	Yes	24/24 GTR (100%)	13.3 months (mean; range 0.4-42.4)	9/14 metastasis patients with symptomatic improvement by last follow up (64%). Among metastases, median time to steroid freedom of 3.4 weeks.	None
Rahmathulla G, et al. (2012)	Brain metastases	LITT (N=1)	20mm maximal diameter	Yes (needle biopsy)	N/A	7 weeks	Complete steroid wean with near resolution of symptoms	None
Rao MS, et al. (2014)	Brain metastases	LITT (N=15)	3.7 cm^3 (mean; range 0.5-25.5)	No: mixed group of pure RN and admixed RN+viable tumor, proportion not reported	N/A	24 weeks (median; range: 4-84)	5/8 symptomatic patients with improvement (63%), 1 with worsening (13%). 2/16 suffered subsequent recurrence requiring craniotomy, of which both were pathologically-confirmed RN (13%).	Asymptomatic hemorrhage, new hemiparesis (N=1 each)
Sujijantarat N, et al. (2020)	Brain metastases	LITT (N=25), bevacizumab (N=13)	2.2 cm^3(median; range 0.3-12.6)	Yes (LITT cases only)	N/A	110 weeks (median; range 23-370)	LITT cohort: 9/13 symptomatic patients with improvement by 6 months (69%). Steroid dependency decreased from 56% to 32% at last follow up. Transient lesion enlargement through month 3 followed by reduction (enhancement	LITT cohort: Confusion and headache, worsening left-sided paresis, seizure, deep venous thrombosis (N=1 each)

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Authors (year)	Diagnoses included	Treatment	Preoperative tumor volume	Pathologic confirmation of RN	Extent of resection	Follow up duration	Outcomes	Periprocedural complications
							evaluated only). N=5 required salvage bevacizumab therapy.	
Current study	Brain metastases	Resection (N=46)	10.5 cm^3(median; range 0.4-31.1)	Yes	27/46 GTR (59%); 19/46 STR (41%)	23 months (median; range 6-31)	23/42 with improved symptoms at 3 months (55%); 15/42 stable (36%). Steroid dependency reduction from 54% to 15% at 1 year. Radiographic edema reduction was greater in the GTR cohort.	Worsened preexisting focal deficit (N=1). 3 patients required repeat craniotomy for refractory RN.