Outcomes of Management of Progressive Radiosurgery-Treated Brain Metastasis With Resection Followed by Pathology-Informed Management: A Retrospective Study

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BACKGROUND AND OBJECTIVES: In patients treated with stereotactic radiosurgery (SRS) for brain metastases, follow-up imaging demonstrating progression may result from treatment effect/radionecrosis (RN) or tumor progression. We report long-term outcomes for a cohort of patients who demonstrated radiological progression on serial imaging after initial radiation and who underwent resection, at which point histology informed further management.

METHODS: A retrospective chart review identified 76 patients with an associated 82 brain lesions between 2009 and 2022, that were initially treated with SRS, and then demonstrated suspicious imaging developing through at least 2 scan time points with either pathologic confirmation of tumor or RN.

RESULTS: Of the 82 lesions, 55 lesions (67.1%) were found to be tumor and were treated with repeat radiation and 27 (32.9%) were found to have pathologically confirmed RN and conservatively managed. 14/27 lesions ultimately found to be radionecrotic required steroids preoperatively due to neurological symptoms. None of these lesions required further intervention with median postsurgery follow-up of 24.4 months (range 1-104 months). There were 55 instances (in 51 patients) of confirmed recurrent/progressive tumor who we treated with repeat aggressive radiation with either Cs-131 brachytherapy (12 [21.8%]) or SRS (43 [78.2%]). Among patients treated with reirradiation, the median follow-up to local failure was 15.2 months (95% CI 7.3-26.6 months). The 2-year local control rate was 79.5% (95% CI 68.3%-92.5%).

CONCLUSION: These results support resection of radiosurgery-treated lesions with progression continuing through serial imaging, and this pathology-informed management results in excellent control of both RN and tumor progression after radiosurgery.

KEY WORDS: Stereotactic radiosurgery, Brain metastases, Radiation necrosis, Imaging

Stereotactic radiosurgery (SRS) for brain metastasis has developed as a standard of care for a large proportion of patients with brain metastases as survival is similar to whole brain radiotherapy with improved quality of life and cognitive outcome. However, prospective randomized trials show a local failure rate upward of 27%-33% based purely on imaging progression after treatment. Management is often complicated due to imaging progression that may represent an effect of treatment or necrosis rather than actual tumor progression. A challenge in optimal management of the radiosurgery-treated patients is that imaging progression from actual tumor growth or occurring consequent to the effects of radiation can be indistinguishable

ABBREVIATIONS: BED, biologic effective dose; **LITT,** laser interstitial thermal therapy; **OS,** overall survival; **PTV,** planning target volume; **RN,** radionecrosis; **SRS,** stereotactic radiosurgery; **WBRT,** whole brain radiation.

using standard MRI imaging. Our group and others have previously demonstrated 30% to 37% of lesions with imaging progression demonstrate surgical pathology of treatment effect or necrosis rather than active tumor[1,2] Although promising techniques are under study to noninvasively distinguish these processes, no techniques have been shown to be sufficiently accurate to guide selection of those who may benefit from further radiation for actual progression from those who may have imaging changes representing an effect of prior treatment.[3]

For this reason, we implemented treatment approach of conservative management of brain metastasis showing imaging using serial MRI to confirm progression and then using surgical resection to determine pathology when the process continues to progress and/or cause significant symptoms. The objective of surgery was to confirm pathology of progressive tumor before administering additional radiation, remove the progressive lesion whether recurrent tumor or necrosis, and facilitate further radiation if warranted by removing much of the previously radiated area as an incidental effect of removing the imaging abnormality. Patients with tumor present were treated with repeat radiosurgery or Cs-131 brachytherapy, and those with no evidence of tumor were conservatively followed without further intervention.

Here, we report the safety and outcome for those patients selected for resection for imaging progression. Further management was guided by pathology with repeat aggressive localized radiotherapy for pathologically confirmed progressive/recurrent tumor after prior radiosurgery and observation for pathologically confirmed radiation necrosis/treatment effect.

METHODS

With institutional review board approval, we conducted a retrospective chart review from an electronic medical record of patients who underwent resection after imaging resection of at least 1 radiosurgery-resected brain metastasis between 2013 and 2020. Given the retrospective nature of the study and use of deidentified data, patient consent was not required. Patients were considered to have progressive or recurrent tumor if any tumor cells were detected in the specimen and radiation effect if there was none. Variables collected include patient age, sex, histology, location of brain metastasis, initial date and dose fractionation of SRS, surgery date, repeat date, and dose of radiation. After repeat radiation, variables collected for toxicity included use of steroids within 3 months of repeat radiation; evidence on chart review of grade 3 or 4 neurotoxicity, defined by chart review; imaging evidence of radiation necrosis or tumor progression; and pathological evidence of radiation necrosis or tumor progression.

Treatment information was obtained from dosimetry review using the treatment management software including MultiPlan (Cyberknife) for SRS and VariSeed (Varian ®) for brachytherapy. SRS treatment was delivered through robotic radiosurgery, and dose was dependent on clinical judgment of provider. Intracavitary brachytherapy was delivered with cesium-131 seeds. Planning target volume (PTV) was abstracted from the finalized radiation plan for lesions treated with SRS (Figures 1 and 2).

Biologic effective dose (BED) calculation was conducted on all SRS plans and brachytherapy plans to compare between different dose fractionations and treatment types. The following equations were used:

$$BED(brachy) = D\left(1 + \left(\frac{\lambda}{(\lambda+\mu)}\right)\frac{D}{\alpha/\beta}\right),$$

$$BED(SRS) = D\left(1 + \frac{d}{\alpha/\beta}\right)$$

where D = total absorbed dose, λ = half life of isotope, μ = repair rate, d = dose, α/β = alpha beta ratio.

In addition, we report the outcome for those patients who had imaging suspicious for progression and were determined to be radionecrosis. These patients were observed after resection. BED1 is defined in this study as the biologic-equivalent radiation dose delivered during primary radiosurgery, and BED2 is defined as the biologic-equivalent dose delivered during reirradiation.

Statistical Analysis

Statistical analysis was completed using STATA 15 (StataCorp 2017), and statistical significance was ascertained with the threshold of $P < .05$. Primary outcome measures for patients with pathologically confirmed recurrent tumor were defined as (1) local recurrence, defined as pathologic evidence of tumor progression in a previously treated site; (2) progression-free survival (PFS), with events including distant metastases, progression in marginal site, or death; and (3) overall survival (OS), which was defined as any cause of death. Secondary outcome measures were prevalence of toxicities as measured

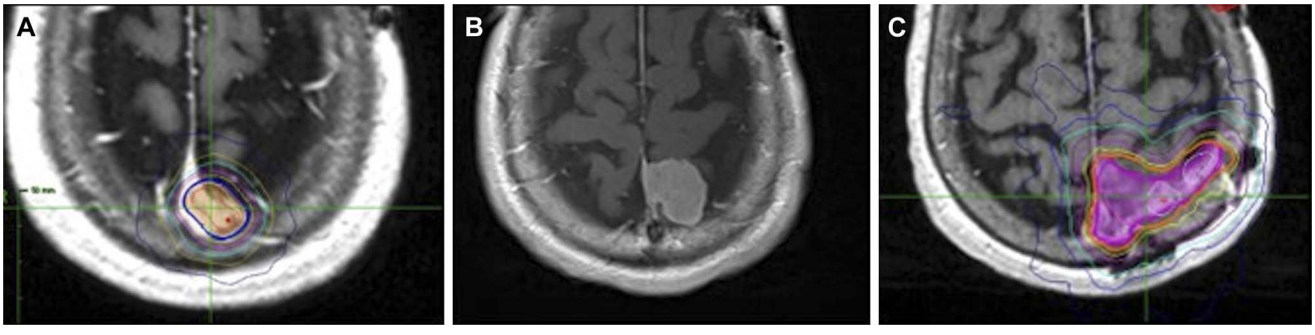

FIGURE 1. A, *Initial SRS volume;* B, *interval MRI showing progression;* C, *and postresection repeat SRS target volume in a single patient. SRS, stereotactic radiosurgery.*

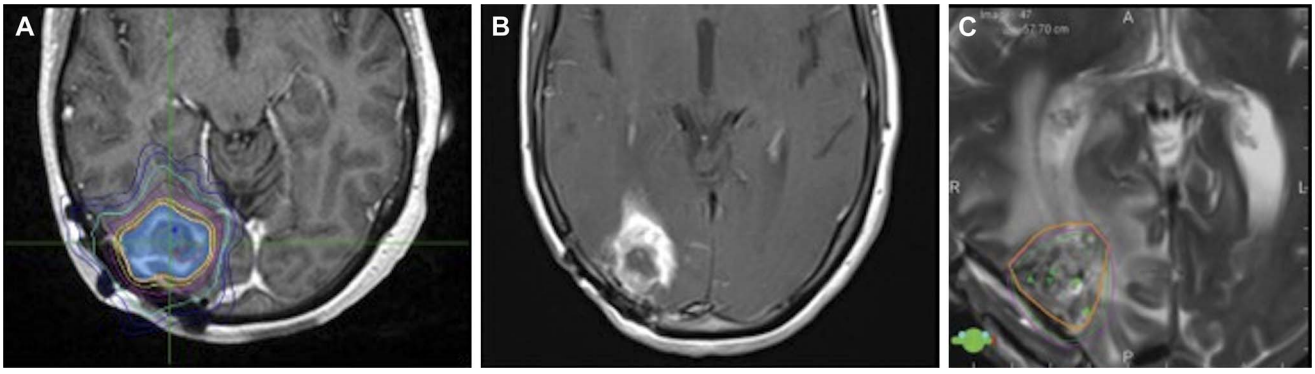

FIGURE 2. A, *Initial stereotactic radiosurgery volume;* B, *interval MRI showing progression; and* C, *postresection brachytherapy volume in a single patient.*

by (1) use of steroids within 3 months, (2) imaging evidence of radiation necrosis or progression, and (3) grade 3 or 4 neurotoxicity as defined by Common Terminology Criteria for Adverse Events v 5.0.[4]

The primary outcome for patients without evidence of tumor in their surgical specimen was absence of intervention for further imaging progression. Potential variables affecting OS, PFS, and toxicity were compared through the Fisher exact test. PFS was calculated using a competing risks analysis. Cox regression analysis was used for calculating OS, LF, and PFS. Time to death was calculated from the last known intervention (repeat radiation (SRS2) through brachytherapy or radiosurgery) for all primary endpoints. Multivariate logistic regression was used for evaluating the impact of sociodemographic and clinical variables on the outcome of our secondary outcome measures.

RESULTS

Patient and Tumor Characteristics

A retrospective chart review identified 76 patients and 82 brain lesions selected for surgery for imaging progression. 55 lesions (67.1%) were found to be true tumor, which was followed by reirradiation, and 27 (32.9%) were found to have radiation effect (Figure 3). Among all 82 lesions, 67 (81.7%) had at least 2 sequential MRIs demonstrating continuing progression between SRS and surgery before surgical intervention.

Radiation Necrosis After Initial Radiation (SRS1)

Among the 27 patients with lesions that were found to have radionecrosis (RN) after the initial radiation, the most common dose fractionation regimen for the prior treatment was 20 Gy in 1 fx (n = 11, 40.7%) with median BED10 reported as 50.4 Gy (IQR 41.6-50 Gy). 12/27 lesions (40.0%) required the use of steroids due to radionecrotic symptoms before surgery whereas the rest were asymptomatic. None of these patients required further intervention at the site of the resected RN, with median follow-up of 35.27 months. Two-year OS for this patient population is 70.4% (Figure 4). Bevacizumab was not used.

Patients With Progressive Tumor After Initial Radiation

Among all 76 patients with 82 brain lesions, 51 patients had an associated 55 instances of brain metastases that were treated once with SRS, recurred locally, underwent resection and repeat aggressive radiation with either brachytherapy or SRS. Most patient population was male (66.6%), with median age at first SRS of 56.3 years (Table 1). Primary histology was non–small-cell lung cancer in 19 cases (37.2%) and breast cancer in 12 cases (23.53%). 10 individuals had previous whole brain radiation (WBRT, 19.5%). Four individuals each had 2 lesions that were reirradiated for local recurrence.

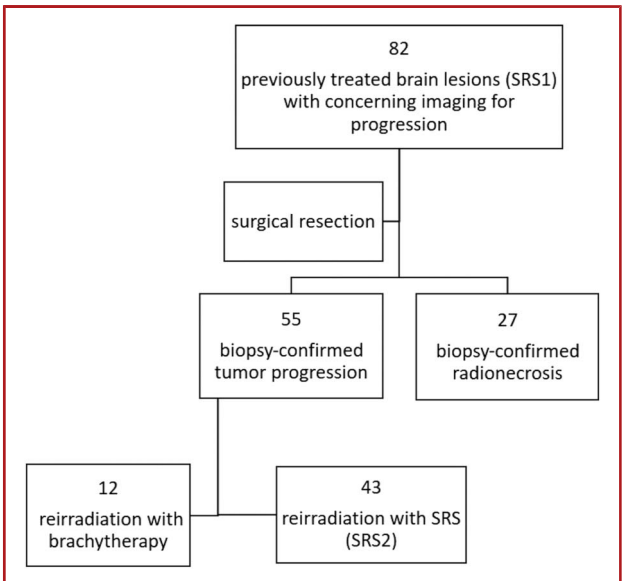

FIGURE 3. *CONSORT diagram of patients evaluated in this study. Patient and lesion characteristics are specific to those patients with biopsy-confirmed tumor progression. SRS, stereotactic radiosurgery.*

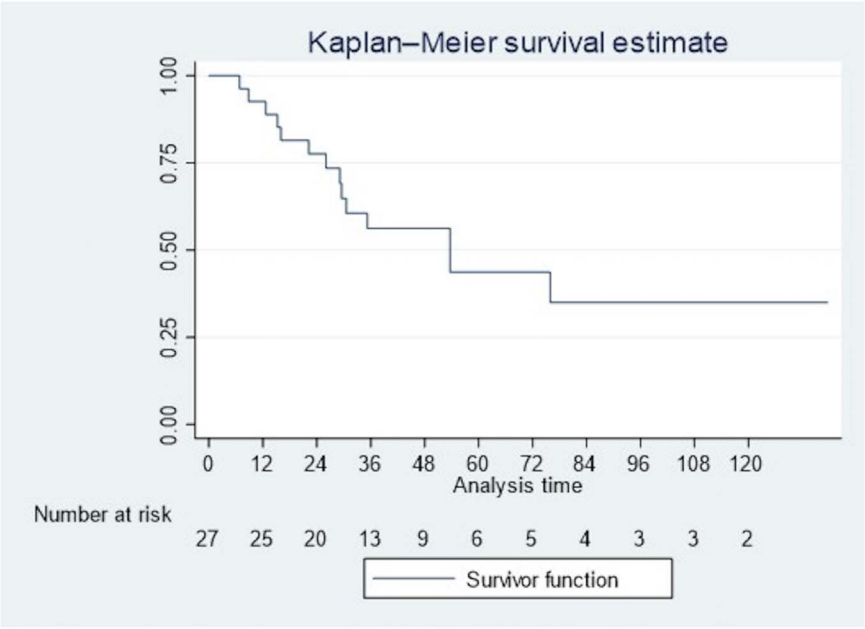

FIGURE 4. *Overall survival of patients with suspicious brain imaging found to have radionecrosis after initial radiation.*

Treatment Characteristics for Progressive Tumor

Reirradiation after pathological confirmation of recurrent tumor (55 brain lesions) included brachytherapy with Cesium-131 or repeat SRS. Forty-three of lesions (78.2%) were treated with repeat SRS, while 12 lesions (21.8%) were treated with brachytherapy. Most common fractionation for repeat irradiation with SRS was 8 Gy × 3 fx (n = 15, 27.3%), followed by 5 Gy × 5 fx (n = 10, 18.2%) and 4 Gy × 5 fx (n = 8, 14.6%). Brachytherapy prescribed absorbed dose was 60 to 65 Gy (BED10 of 61-66 Gy) to a depth of 5 mm, with number of seeds and seed activity placed to achieve this objective based on an algorithm provided by Isoray. Initial PTV volume ranged from 0.129 to 52.1 cc, and median volume was 5.75 cm^3. Repeat PTV volume, among those that were reirradiated with SRS only, was between 0.84 and 387 cm^3, with a median of 16.4 cm^3. IQR of BED10 of initial radiation was 41.6 to 50.4 Gy (median 48 Gy) and for repeat radiation was from 35.7 to 43.2 Gy with median BED10 as 37.5 Gy (Table 2).

Overall Survival, Local Failure, and Toxicity Outcomes

Twenty-five lesions after reirradiation caused the individual to require the use of steroids (45.4%) in both the brachytherapy and SRS groups, 21.8% experienced evidence of grade 3 or 4 neurotoxicity, 29.0% (n = 16 lesions) had further imaging progression after repeat radiosurgery. Of these 16 lesions, 4 had pathological evidence of RN, 6 had pathological evidence of treatment effect (including abscess, fibrous tissue with calcifications, or increasing edema), and 4 had pathological evidence of progressive disease (1 of which was a marginal failure, and 1 patient who passed away before further interventions could be done). The remaining 2 patients were lost to follow-up. Crude rate of RN in this population is thus 4/55 lesions (7.2%). Encapsulating all treatment effect post reirradiation (including those without pathological confirmation), the proportion is 10/55 lesions (18.2%). Given the limited number of brachytherapy procedures, we cannot make conclusions about the relative benefits of brachytherapy vs SRS (Table 3).

Overall Survival Among All Patients Since Second Radiation

Among 47 patients who each had only 1 lesion, the median time from the date of second radiation (through radiosurgery or brachytherapy) to death was 15.2 months (95% CI 7.9-26.8 months). Patients with >1 lesion were excluded for survival analysis. The 1-year and 2-year OS rates were 61.7% (95% CI 48.9%-77.9%) and 52.0% (95% CI 39.0%-69.3%), respectively. On univariate Cox regression analysis considering BED2, age at reirradiation, sex, prior WBRT, prior surgery, SRS2 PTV volume, and lesion location, no factors were associated with OS.

Overall Survival Among all Patients since Second Radiation by Type of Reirradiation

Among patients treated with RS for reirradiation, the median follow-up to death was 18.3 months (95% CI 7.3-32.5 months). The 1-year and 2-year OS rates among patients treated with rSRS for reirradiation were 67.3% (95% CI 53.0%-85.3%) and 57.3% (95% CI 42.5%-77.3%), respectively.

Among patients treated with brachytherapy for reirradiation, the median follow-up to death was 9.7 months (95% CI 3.9-85

TABLE 1. Demographics of Patients With Pathological Confirmation of Progressive Tumor

No. of patients	N = 51	%
Sex		
Male	34	66.6
Female	17	33.3
Median age at SRS1	56.3	
Median age at SRS2 or brachytherapy	58.2	
Histology		
Nonsmall cell lung cancer	19	37.2
Breast	12	23.53
Melanoma	4	7.84
Endometrial	3	5.88
Renal cell carcinoma	2	3.92
Small cell lung cancer	3	5.88
Thyroid	2	3.92
Other	6	11.7
Prior whole brain radiation		
Y	7	13.7
Y (PCI)	3	5.8
N	41	80.39
Time intervals between SRS series		
<1 year	25	45.45
1-2 years	16	29.09
2-3 years	10	18.18
3-4 years	3	5.45
4+ years	1	1.82

SRS, stereotactic radiosurgery.

TABLE 2. Characteristics of Lesions With Confirmed Tumor after SRS1

No. of lesions	N = 55	%
Location		
Frontal	18	32.4
Parietal	12	21.8
Temporal	8	14.6
Occipital	7	12.7
Cerebellum	10	18.2
Histology		
Nonsmall cell lung cancer	20	36.4
Breast	13	23.6
Melanoma	4	7.3
Endometrial	3	5.5
Renal cell carcinoma	2	3.7
Small cell lung cancer	5	9.1
Thyroid	2	3.7
Other	6	10.9
SRS1 PTV volume (cm^3)		
Mean (SD)	10.7 (13.4)	—
Median (IQR)	5.8 (0.7-16.2)	—
SRS2 PTV volume (cm^3)[a]		
Mean (SD)	31.4 (59.6)	—
Median (IQR)	16.4 (10.7-30.2)	—

PTV, planning target volume; SRS, stereotactic radiosurgery.
[a]PTV volume unavailable for brachytherapy.

months). The 1-year and 2-year OS rates among patients treated with brachytherapy for SRS2 were 45.5% (95% CI 23.8%-86.8%) and 36.4% (95% CI 16.6%-79.5%), respectively (Figure 5).

Local Control Among All Patients Since SRS2 or Brachytherapy

The median follow-up from date of reirradiation to local failure was 14.1 months (95% CI 7.6-24.3 months). The 1-year and 2-year local control rates were both 79.5% (95% CI 68.3%-92.5%). On univariate Cox regression analysis considering BED2, age at SRS2, sex, prior WBRT, prior surgery, SRS2 PTV volume, and lesion location, BED2 was associated with less local failure outcomes (HR [hazard ratio] 0.90, $P = .045$).

Local Control Among All Patients Since Reirradiation, Stratified by Type of Reirradiation Treatment

Among patients treated with SRS for reirradiation, the median follow-up to local failure was 15.2 months (95% CI 7.3-26.6 months). The 2-year local control rates among patients treated with re-SRS and for brachytherapy for reirradiation were both 79.5% (95% CI 67.0%-94.4%). Among patients treated with brachytherapy for reirradiation, the median follow-up to local failure was 11.0 months (95% CI 3.9-41.3 months).

In a subgroup univariate Cox regression analysis of patients treated with re-SRS considering BED2, age at SRS2, sex, prior WBRT, prior surgery, SRS2 PTV volume, and lesion location, BED2 was associated with less local failure outcomes (HR 0.88, $P = .045$) (Figure 6).

TABLE 3. Toxicity by Method of Reirradiation (by Lesion) Among Patients With Confirmed Tumor After SRS1

	SRS2 (n = 43)		Brachytherapy (n = 12)		Total (n = 55)	
Use of steroids within 3 months of reirradiation	22	51.2%	3	25.0%	25	45.4%
Evidence of grade 3 or 4 neurotoxicity as per chart review	11	25.6%	1	8.3%	12	21.8%
Imaging evidence of necrosis or progression after retreatment	14	32.5%	2	25.0%	16	29.0%
Pathological evidence of radiation necrosis	4	9.3%	0	0%	4	7.2%
Pathological evidence of tumor progression	2	4.6%	2	16.7%	4	7.2%

SRS, stereotactic radiosurgery.

Associations With Grade 3 or 4 Neurotoxicity

On univariate logistic regression analysis considering BED1, BED2, age, sex, prior WBRT, prior surgery, SRS1 PTV volume, SRS2 PTV volume, and lesion location, no factors were associated with grade 3 or 4 neurotoxicity.

DISCUSSION

Brain metastases are overall the most prevalent intracranial tumor in adults; with conservative estimates suggesting that 10%-20% of patients with non–central nervous system primary cancers

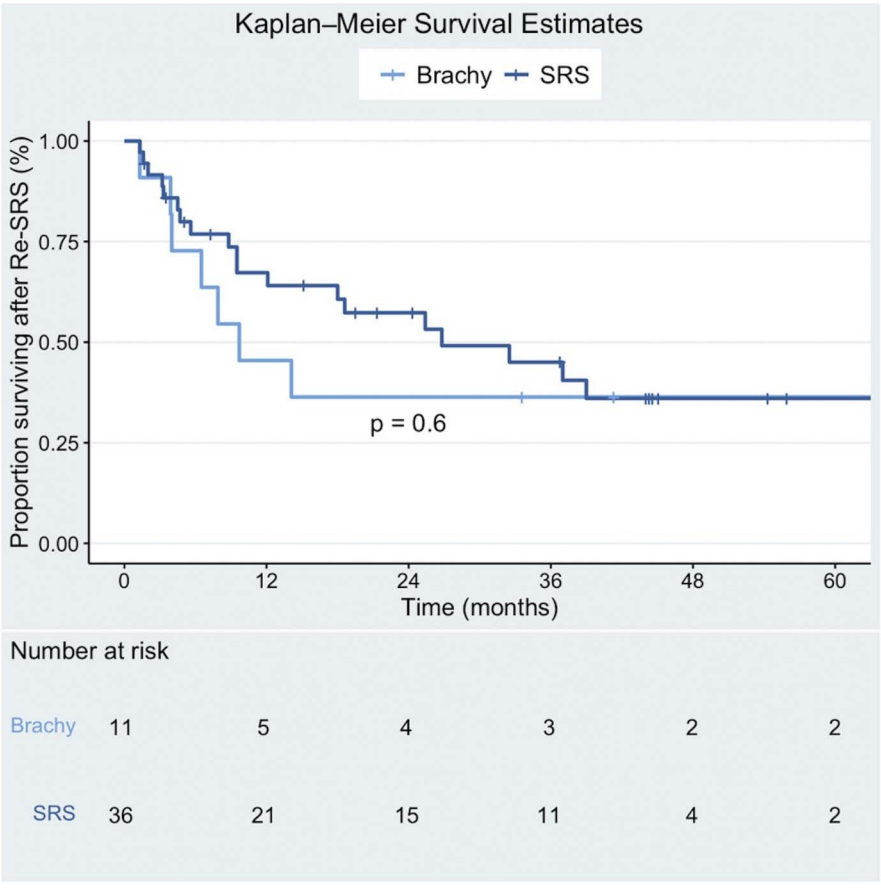

FIGURE 5. *Overall survival curve among patients with local recurrence of brain metastases who received re-irradiation with either brachytherapy and SRS2. SRS, stereotactic radiosurgery.*

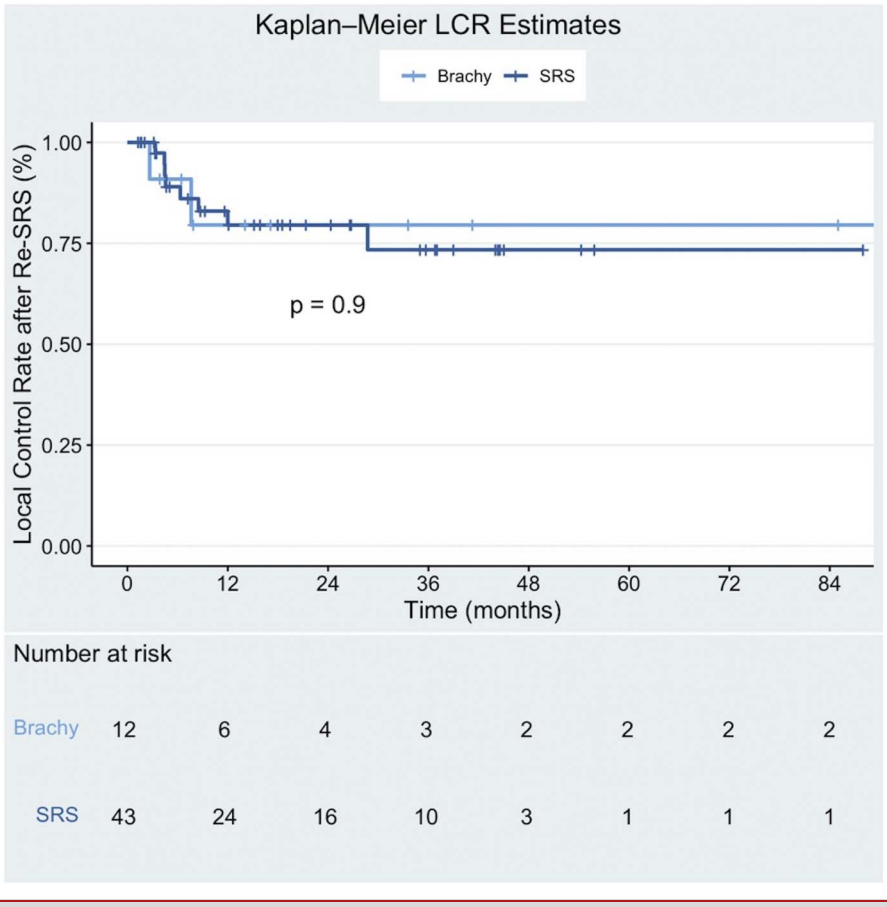

FIGURE 6. *Local failure among patients with local recurrence of brain metastases who received reirradiation with either brachytherapy or SRS2. SRS, stereotactic radiosurgery.*

will develop eventual intracranial metastatic disease.[5,6] There is an increased need for strategies to optimize control of brain metastasis that progress after prior aggressive local therapy with SRS.

Stereotactic radiosurgery is an attractive therapy in the treatment of patients with limited intracranial disease burden at presentation, increasing both local control and OS. Management has not been optimized for patients who experience imaging progression of a previously stereotactically treated brain metastasis, though prior studies have shown efficacy with reirradiation. Indeed, reirradiation to metastases previously treated with initial definitive SRS results in radiation necrosis in up to 30% of patients within a year of post-treatment.[7-13] The high risk of necrosis may relate not only to the risks of repeat aggressive radiation administered to the same area but also to the possibility that the original imaging changes are the result of radiation injury which is indistinguishable from progressive tumor on standard MRI.

Although most series determine the presence of radiation necrosis or true progression based on consensus evaluation of MRI imaging, we have found that blinded radiologist evaluation had sensitivity and specificity of 97% and 19%, respectively, when correlated with ground truth determination by pathology.[1] In prior work by this group, a machine learning model based on a combination of radiomic features, connectomic patterns, and clinical factors had sensitivity, specificity, and area under the curve of 0.87, 0.84, and 0.89.[14] This has not, however, been tested yet with a validation data set. A recent review has comprehensively evaluated studies that have used MRI and nuclear medicine–based approaches and concluded that the evidence is not yet sufficient to support the routine implementation of any of noninvasive approaches.[3] Laser interstitial thermal therapy (LITT) has also been used after SRS to treat both tumor and/or RN. In a review of these studies, Srinivasan et al[15] determined factors in favor of LITT for recurrent metastatic lesions (surgically inaccessible, supratentorial lesions, less significant preoperative symptoms). In addition, LITT has been studied for use after RN as well, with the advantage of cytoreduction and combination of needle biopsy. LITT was not used in the patient population of this study but remains a treatment under investigation.

In this context of uncertain meaning of post-treatment imaging changes, we adopted a policy of repeat resection for a continuing progressive process on serial imaging and/or a process causing symptoms not resolving with steroids. Surgical resection had the aim of obtaining pathological diagnosis to guide further intervention and for therapeutic benefit. In addition, there is evidence that interval surgical resection of the previously irradiated lesion before retreatment with SRS may be associated with reduction of RN risk.[8] Resection was an effective treatment for treatment effect/necrosis with no patient requiring further intervention during the period of follow-up.

Pathology-informed management was effective at achieving the primary goal of local control of the effected lesion. For the group of patients with imaging progression after the initial radiation determined to be RN, local control of affected lesion was 100%. For the group of patients with imaging progression after the initial radiation determined to be tumor progression, local control at the site of the affected lesions at 2 years was 79.5% (95% CI 68.3%-92.5%). Both SRS and brachytherapy were similarly effective. Recently, Imber et al demonstrated safety and efficacy of using ^{131}Cs seeds prescribed to 60 Gy at 5 mm from a previously irradiated cavity after a resection. Though a limited follow-up time (median 1.6 years), they demonstrated a local progression rate of 8.4%.[16] For repeat SRS local control, Loi et al completed a recent systematic review reviewing repeat irradiation for brain metastatic lesions with SRS. Reported 1-year local control across 11 studies fell between 61% and 81%; similarly, our 1-year local control rate was >75% for both SRS and brachytherapy.

Patients who developed RN after first SRS had a 2-year OS of 70.4% (calculated from the date of first intervention). Among patients with true progression of tumor and reirradiation after surgical resection of a radiated metastatic brain lesion, we noted an OS at 2 years of 52.0% (calculated from the date of second intervention). At 2 years, there was a significant difference in OS between SRS and brachytherapy (57.3% at 2 with SRS and 36.4% with brachytherapy), which may reflect unknown selection criteria. This difference did not persist past 3 years.

The toxicity of reirradiation after repeat SRS or brachytherapy seemed appropriate. Fifteen lesions underwent a second resection for imaging progression RN after repeat radiation, and only 4 had pathological evidence of RN, 6 had true progression, and 5 had "treatment effect" without evidence of tumor or frank necrosis. Prior reported crude RN rates have a wide range from 0% to 30%,[10] although generally not measured with pathological confirmation. We calculated BED to compare brachytherapy and SRS across different radiation fractionations and treatment types. Higher BED was associated with better OS (HR 0.91, $P = .045$). We believe the risk of radiation necrosis of 7.2% in this population is appropriate given the presence of confirmed recurrent tumor requiring treatment for control.

A unique advantage of this study is that the cause of imaging progression was confirmed by pathology in all cases. This is currently the gold standard for diagnosis given the limitations of imaging or clinical criteria that distinguishes radiation necrosis from true tumor progression.[1,17-19]

Limitations

Limitations of the study include limited reliable information to determine exact indications of surgical repeat resection but likely due to imaging or symptomatic progression. Risks of surgery and appropriate selection for surgery are critical and were conducted by the provider team. In addition, there are limited data to describe outcome for patients who did not have surgery at the time of suspected progression, which may occur because the patient was not a surgical candidate, the process stabilized, or other unknown selection factors. Data on surgical complications were not collected. The choice of brachytherapy or radiosurgery was based on the preference of the treating physicians without clear selection criteria. Only 21.8% (n = 12 lesions) were treated with brachytherapy, such that conclusions guiding the choice of options are not possible. Finally, outcome may be affected by systemic therapies also received by the patients which cannot be evaluated given the heterogeneous patient population and wide span of years.

CONCLUSION

Surgery was a successful intervention for patients with progressive MRI imaging changes after radiosurgery that verifies that pathological cause and thereby informs subsequent management. For those with progressive tumor, control was achieved for 79.5% of lesions 2 years with reirradiation of the resection bed even though these patients were treated for progression after prior radiosurgery. For the 32.9% of all lesions with resected necrosis/treatment effect, further intervention was not needed.

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Disclosures

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COMMENTS

The authors report their findings in 76 patients with 82 metastatic tumors that were removed after stereotactic radiosurgery because of enlargement on MRI. Two out of 3 lesions were progressive tumor and were treated with repeat SRS. One obvious question relates to the use of laser interstitial thermal therapy, which has been shown to be a useful therapy for persons with tumor progression **or** radiation necrosis after SRS. LITT is less invasive than craniotomy and can provide a definitive treatment that would avoid the need for a second SRS. In addition, most readers probably will use various imaging techniques including MR spectroscopy, MR perfusion, contrast clearance analysis, and/or FDG PET to differentiate between tumor and radiation necrosis. These methods are not definitive (which is why there are so many of them) but can often help patients avoid surgery when lesions are not causing symptoms or of a threatening size.

The main "moral" of this story is that neurosurgeons should take seriously when follow-up imaging shows signs of tumor growth after SRS, and to consider surgery so that the appropriate diagnosis can be made, and treatment provided.

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