

Outcomes of Repeat Stereotactic Radiosurgery for Locally Recurrent Brain Metastases Following Initial Stereotactic Radiosurgery

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Abstract

Background

Local recurrence after stereotactic radiosurgery (SRS1) for brain metastases remains a therapeutic challenge, and optimal re-irradiation parameters are not well defined. This study evaluated local control (LC) and predictors of radiation necrosis (RN) following repeat stereotactic radiosurgery (SRS2) for previously irradiated brain metastases.

Methods

This retrospective study included patients treated with SRS2 for locally recurrent brain metastases after prior SRS1. Patients who had received whole-brain radiotherapy were excluded. Follow-up MRI scans were reviewed for LC and RN according to RANO criteria. Kaplan–Meier analysis was used for LC and RN-free survival. Cox regression analysis identified predictive factors. ROC curve analysis determined optimal dosimetric cut-off values.

Results

Forty patients with 59 locally recurrent brain metastases treated with SRS2 to the same lesion were analyzed. Median follow-up was 11 months (range, 2–83). Median SRS2 prescription dose was 24 Gy (range, 14–35) delivered in a median of 3 fractions (range, 1–5), and median GTV diameter was 2.1 cm (range, 0.3–7.6). One-year local progression-free survival was 57.5% while one-year RN-free survival was 80%. Higher SRS2 EQD₂(10) (> 33.6 Gy; 63.8% vs 93.1%, $p = 0.007$), cumulative EQD₂(10) (> 75 Gy; 63.2% vs 91.4%, $p = 0.006$), SRS2 BED₁₀ (> 83.7 Gy; 65.8% vs 90.9%, $p = 0.013$), and cumulative BED₁₀ (> 177 Gy; 65.2% vs 91.0%, $p = 0.013$) were associated with significantly increased RN risk without corresponding LC benefit. Age, sex, histology, location, prior surgery, GTV and PTV diameter and volume, SRS1–SRS2 interval, dosimetric indices, and systemic therapy were not significantly associated with LC or RN.

Conclusions

Repeat SRS is an effective and well-tolerated salvage treatment for locally recurrent brain metastases. Doses below the identified BED and EQD₂ thresholds were associated with a lower risk of RN without significantly compromising local control. Prospective studies are warranted to validate optimal re-SRS dose constraints and treatment strategies for recurrent brain metastases.

BACKGROUND

Brain metastases represent the most common intracranial malignancy in adults, developing in approximately 10–40% of cancer patients during their disease course ^{1,2}. The management of brain metastases has evolved considerably over the past two decades, driven by improvements in systemic therapy and advances in neuroimaging. Current guidelines recommend stereotactic radiosurgery (SRS) as the preferred first-line local treatment for patients with a limited number of brain metastases, with avoidance of whole-brain radiotherapy (WBRT) in this setting ^{3–5}.

SRS achieves local control (LC) in approximately 80–90% of treated lesions depending on tumor histology, lesion size, and delivered dose ⁶. The optimal salvage strategy following SRS failure remains an unresolved question and depends on several factors, including the anatomical location and size of the lesion, previous treatment, patient performance status, and anticipated survival. Available options include surgical resection, laser interstitial thermal therapy (LITT), systemic therapies, intraoperative radiotherapy (IORT), brachytherapy, salvage WBRT, and repeat SRS (reSRS) ^{7–9}. Among these, reSRS has gained increasing interest given the well-recognized neurocognitive consequences of WBRT and the limited candidacy for surgery in many patients.

ReSRS to the same lesion carries a theoretically higher risk of radiation necrosis due to cumulative dose exposure in previously irradiated brain parenchyma ¹⁰. Nevertheless, a growing body of retrospective data suggests that reSRS can achieve adequate LC with an acceptable adverse event (AE) rate with a considerable heterogeneity in patient selection, lesion characteristics, dosimetric parameters, and definitions of response and AE ^{10–32}. Furthermore, limited data are available regarding cumulative biologically equivalent dose (BED) threshold values associated with radionecrosis (RN) after reSRS. Identification of clinically relevant dose constraints remains challenging because of substantial heterogeneity in treatment techniques, fractionation schedules, and outcome definitions across published series.

In this study we present the outcomes of our patients who underwent reSRS for locally recurrent brain metastases following initial SRS, aiming to contribute to the optimization of patient selection criteria and dose-fractionation regimens for reSRS treatment.

METHODS

Patient Selection. This was a single-institution, IRB-approved retrospective cohort study. Adult patients (age ≥ 18 years) who received more than one course of intracranial SRS -single or multiple fractionated- to brain metastases between January 2015 and March 2025 were included. A total of 577 patients underwent repeat intracranial radiation therapy. Patients who underwent a second course of SRS (SRS2) directed to the same metastatic lesion that had been treated with the initial SRS (SRS1) were identified. Patients with resection cavity SRS were included. Patients with any prior WBRT—whether before SRS1 or in the interval between SRS1 and SRS2—were excluded. The SRS1 planning target volume (PTV) and the SRS2 gross tumor volume (GTV) were co-registered using rigid image fusion on planning CT datasets. Lesions were included only when both volumes demonstrated anatomical overlap according to the

ESTRO definition of Type 1 reirradiation³³. Patients were treated using Varian TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, CA, USA), Accuray CyberKnife (Accuray Inc., Sunnyvale, CA, USA), or Elekta Leksell GammaKnife (Elekta AB, Stockholm, Sweden).

Dosimetric Analysis. Treatment planning data were extracted from the treatment planning system for both SRS1 and SRS2. Parameters collected included lesion volume, PTV margin, prescription isodose volume (PIV), target volume covered by PIV (TV_PIV), homogeneity index (HI), gradient index (GI), new Paddick conformity index (nCI), maximum dose within the PTV (Dmax) and brain dose–volume histograms. All doses were converted to biologically equivalent doses (BED) and equivalent doses in 2-Gy fractions (EQD₂) using the linear-quadratic model, with $\alpha/\beta = 10$ Gy for tumor and $\alpha/\beta = 3$ Gy for normal brain tissue. Cumulative SRS1 + SRS2 BED₃, BED₁₀, EQD₂ (3) and EQD₂(10) values were calculated for each lesion.

Outcome Assessment. Patients were followed with brain MRI scans at 6–12-week intervals, incorporating at minimum T1, T1 post-contrast, and T2/FLAIR sequences. Response was assessed according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria³⁴. Local recurrence was defined as a $\geq 20\%$ increase in the longest diameter of the target lesion on serial imaging. Multiparametric MR and/or PET/CT imaging were used, when necessary to confirm progression or radiation related changes. Transient lesion enlargement followed by spontaneous regression was not classified as recurrence. Adverse events (AE) were graded per the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). RN was graded using the International Stereotactic Radiosurgery Society (ISRS) classification system³⁵. Advanced imaging (MR perfusion, MR spectroscopy, or PET) was incorporated into clinical decision-making when available, and pathology made the final classification when surgery was performed.

Statistical Analysis. Local progression-free survival (LPFS) and radionecrosis-free survival (RNFS) were analyzed per lesion; overall survival (OS) was analyzed per patient. LPFS time was measured from the start of SRS2 to the date of local progression. OS was measured from the start of SRS2 to the date of last follow-up or death from any cause. Survival outcomes were estimated using the Kaplan–Meier method with 95% confidence interval (95% CI); group comparisons were performed with the log-rank test. Univariate analysis of clinical and dosimetric covariates was conducted for LPFS and RNFS. Variables reaching statistical significance on univariate analysis were entered into a multivariable Cox proportional hazards regression model. For dosimetric parameters associated with RN risk on univariate analysis, receiver operating characteristic (ROC) curve analysis was performed, and optimal threshold values were identified using the Youden index. Statistical significance was defined as $p < 0.05$ (two-sided). All analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient, Tumor and Treatment Characteristics

The study included 40 patients with a total number 59 lesions treated with reSRS following local recurrence. The median number of lesions treated with reSRS per patient was 1 (range, 1–7): 33 patients had 1 lesion, three had 2, and four had between 3–7. A total of 61 treatment sessions were delivered across 40 patients. Among the 59 lesions, 9 (15.3%) at SRS1 and 10 (18.6%) at SRS2 were post-surgical cavities; the remaining lesions were intact metastases.

The median patient age was 56 years (range, 34–89) at the time of SRS1 and 57 years (range, 36–90) at SRS2. The cohort was predominantly female (60%; $n = 24$). Primary tumor origin was lung cancer in 50% ($n = 20$), breast cancer in 27.5% ($n = 11$), colorectal cancer in 10% ($n = 4$), melanoma in 7.5% ($n = 3$), and renal cell carcinoma (RCC) in 5% ($n = 2$). The most frequent brain locations were frontal (32.2%), cerebellar (23.8%), parietal (13.6%), and temporal (13.6%). Lesion morphology at SRS1 was solid in 62.7%, heterogeneous in 16.9%, cavity in 15.3%, and cystic in 5.1%. Seventy percent ($n = 28$) of patients received systemic treatment during SRS1 and SRS2. Patient and lesion characteristics are summarized in Table 1.

The median interval from SRS1 to SRS2 was 11 months (range, 3–43 months); 57.6% of lesions were re-irradiated within 12 months of SRS1.

SRS1. At SRS1, the most frequently used treatment system was a linear accelerator (linac, 71.2%), followed by CyberKnife (25.4%) and GammaKnife (3.4%). The most common fractionation schedules were 3×8 Gy ($n = 14$, 23.7%), 5×5 Gy ($n = 13$, 22.0%), 5×6 Gy ($n = 9$, 15.3%), and 1×20 Gy ($n = 9$, 15.3%). The median total SRS1 dose was 24 Gy (range, 15–30 Gy) delivered in a median of 3 fractions (range, 1–5). Median BED₁₀ was 43.2 Gy (range, 35.7–81.6 Gy), EQD₂(10) 36.0 Gy (29.8–68.0 Gy), BED₃ 90.0 Gy (66.6–216.0 Gy), and EQD₂(3) 54.0 Gy (40.0–129.6 Gy). Median GTV diameter at SRS1 was 1.1 cm (range, 0.2–5.6 cm) and median GTV volume was 0.7 cc (range, 0.1–39.4 cc).

SRS2. The most frequently used treatment system was linac 73%, followed by CyberKnife 25% and GammaKnife 2%. At SRS2, the most common fractionation schedules were 5×5 Gy ($n = 13$, 22.0%), 5×6 Gy ($n = 10$, 17.0%) and 3×8 Gy ($n = 8$, 13.6%). The median total SRS2 dose was 24 Gy (range, 14–35 Gy), in a median of 3 fractions (range, 1–5). Median GTV diameter at SRS2 was 2.1 cm (range 0.3–7.6 cm) and median GTV volume was 2.2 cc (range, 0.1–63.8 cc). Median SRS2 BED₁₀ was 37.5 Gy (21.0–60.0 Gy), EQD₂(10) 31.25 Gy (17.5–50.0 Gy), BED₃ 70.0 Gy (21.0–153.3 Gy), and EQD₂(3) 42 Gy (12.6–92.0 Gy). Cumulative (SRS1 + SRS2) median EQD₂(10) was 71.25 Gy (55.25–108.0 Gy) and cumulative median BED₃ was 174.67 Gy (120.67–306.7 Gy). Treatment parameters are summarized in Table 1.

Table 1
Patient and lesion characteristics and treatment parameters.

Patient n = 40		
Characteristic	Subgroup	n (%) or median (range)
Median age at SRS1 / SRS2 (years)		56 (34–89) / 57 (36–90)
Sex	Female / Male	24 (60%) / 16 (40%)
Primary histology	Lung / Breast / Colorectal / Melanoma / RCC	20 (50%) / 11 (28%) / 4 (10%) / 3 (8%) / 2 (5%)
Median KPS at SRS1 / SRS2		90 (60–100) / 80 (50–90)
Median DS-GPA at SRS1 / SRS2		3.0 (0.5–4.0) / 2.5 (0–4.0)
Lesion n = 59		
Parameter	SRS1	SRS2
Median interval between SRS1 and SRS2 (months)	11 (3–43)	
Lesion morphology (SRS1) Solid / Heterogeneous / Cavity / Cystic	37 (63%) / 10 (17%) / 9 (15%) / 3 (5%)	
Brain location	Frontal / Cerebellar / Parietal / Temporal / Occipital / Other	19 (32%) / 14 (24%) / 8 (14%) / 8 (14%) / 7 (12%) / 3 (5%)
Device (Linac / CyberKnife / GammaKnife)	42 (71%) / 15 (25%) / 2 (3%)	43 (73%) / 15 (25%) / 1 (2%)
Median fractions (range)	3 (1–5)	3 (1–5)
Median total dose, Gy (range)	24 (15–30)	24 (14–35)
Median GTV diameter, cm (range)	1.1 (0.2–5.6)	2.1 (0.3–7.6)
Median GTV volume, cc (range)	0.7 (0.1–39.4)	2.2 (0.1–63.8)
Median BED ₁₀ , Gy (range)	43.2 (35.7–81.6)	37.5 (21.0–60.0)
Median EQD ₂ ₁₀ , Gy (range)	36.0 (29.8–68.0)	31.25 (17.5–50.0)
Median BED ₃ , Gy (range)	90.0 (66.6–216.0)	70.0 (21.0–153.3)
Median EQD ₂ (3), Gy (range)	54.0 (40.0–129.6)	42.0 (12.6–92.0)

Patient n = 40		
Characteristic	Subgroup	n (%) or median (range)
Cumulative EQD ₂ (10) SRS1 + SRS2, Gy (range)	71.25 (55.25–108.0)	
Cumulative BED ₃ SRS1 + SRS2, Gy (range)	174.67 (120.67–306.7)	
Median Dmax, Gy (range)	30.8 (17.2–49.9)	30.2 (17.4–42.6)
Median conformity index (range)	1.3 (1.0–6.0)	1.4 (1.0–2.3)
Concurrent systemic therapy	28 (47.5%)	28 (47.5%)

BED, biologically equivalent dose (α/β indicated by subscript); EQD2, equivalent dose in 2-Gy fractions; GTV, gross tumor volume; Dmax, maximum dose within the PTV. RCC, renal cell carcinoma; KPS, Karnofsky Performance Score; DS-GPA, Diagnosis-Specific Graded Prognostic Assessment.

Survival Outcomes

Overall survival. Median follow-up after SRS2 was 11 months (range, 2–83 months). At last follow-up, 45% of patients (n = 18) had died and 55% (n = 22) remained alive. Median OS from SRS2 was 22 months (95% CI 2–45 months). The estimated 1-, 2-, 3-, and 5-year OS rates from SRS2 were 69.8%, 48.2%, 48.2% and 24.1%, respectively (Fig. 1a). The estimated median OS from SRS1 was 53 months (95% CI 20–86 months), with 1-, 2-, 3-, and 5-year OS rates of 97.5%, 79.7%, 52.8% and 46.2%. Median OS from initial primary cancer diagnosis was 141 months (95% CI 87–195 months). Among histological subgroups, median OS from SRS2 was longest in breast cancer patients (85 months), followed by lung and RCC (16 months each), colorectal (11 months), and melanoma (6 months).

Intracranial distant control. Median intracranial distant metastasis-free survival (iDMFS) from SRS2 was 16 months (95% CI 11–21 months). The 1-, 2-, 3-, and 5-year intracranial iDMFS rates were 59.7%, 43.1%, 25.2% and 8.4%, respectively. New intracranial distant metastases were observed in 25 of 40 patients during follow-up.

Local Progression Free Survival.

Median LPFS was 27 months (95% CI 8–47 months). Local recurrence was observed in 24 of 59 lesions (40.7%). The 1-, 2-, and 3-year LPFS rates were 57.5%, 50.1% and 37.5%, respectively (Fig. 1b). 87.5% of all recurrence events (21/24) occurred within the first year after SRS2.

Radiological response was complete response in 1.7% (n = 1), partial response in 18.6% (n = 11), stable disease in 39.0% (n = 23), and progressive disease in 40.7% (n = 24) of the lesions.

Among lesions with local recurrence, 10 (17.0%) subsequently received a third SRS course, four (6.8%) underwent salvage WBRT, four (6.8%) received systemic therapy, one (1.7%) underwent surgery, and one (1.7%) received combined surgery and WBRT. Leptomeningeal spread was observed in 32.2% (n = 19) during the follow-up period.

Adverse Events

AE was observed in 22% (n = 13): grade 1 in 3.4% (n = 2), grade 2 in 13.6% (n = 8), grade 3 in 5.1% (n = 3), and grade 4 in 1.7% (n = 1). Events included headache, dizziness, nausea/vomiting, focal neurological deficits, seizure, and RN.

Radionecrosis

Incidence and grading. RN was detected in 10 of 59 lesions (16.9%) and in 10 of 40 patients (25%). Symptomatic RN was observed in 8 lesions (13.6%) and 8 patients (20.0%). ISRS grading distribution was grade 1 in 2 (5.1%), grade 2 in 4 (6.8%), grade 3 in 3 (5.1%) and grade 4 in 1 (1.7%). Among histological subgroups, RN occurred in 6 of 20 lung cancer patients (30%), 2 of 11 breast cancer patients (18%), 1 of 4 colorectal patients (25%), 1 of 2 RCC patients (50%), and none of the 3 melanoma patients. The 1-, 2-, and 3-year RNFS rates per lesion were 80.0%, 75.3% and 75.3%, respectively (Fig. 1c). RN occurred within median 5 months (range, 3–16 months). Nine events occurred within the first year after SRS2; 1 was detected at 16 months.

Management. RN was managed with corticosteroids alone in 5 patients (50%), corticosteroids plus bevacizumab in 3 (30%), corticosteroids plus bevacizumab plus *Boswellia serrata* in 1 (10%) and corticosteroids plus bevacizumab plus surgical resection in 1 (10%).

Univariate Survival Analyses

Predictors of LPFS. On univariate analysis, the following variables were significantly associated with inferior LPFS for SRS2: SRS1 DS-GPA score > 2.5 ($p = 0.004$), presence of extracranial metastases at SRS1 ($p = 0.015$), prior SRS history to other brain lesions before SRS1 ($p = 0.019$), radioresistant histology (melanoma or RCC vs others; median local control 9 vs. 27 months; $p = 0.045$), and presence of neurological symptoms at the time of SRS2 ($p = 0.045$). SRS1 Dmax ≤ 30.8 Gy ($p = 0.011$) and SRS1 homogeneity index ≤ 1.3 ($p = 0.01$) were also associated with shorter LPFS. All other tested variables—including sex, age, lesion location, lesion morphology, cavity vs. intact metastasis, SRS1–SRS2 interval, fractionation schedule (single vs. multiple), GTV/PTV diameter and volume at both SRS1 and SRS2, all BED and EQD₂ dose parameters, brain dose–volume histogram parameters, and concurrent or adjuvant systemic therapy—were not significantly associated with LPFS (all $p > 0.05$).

Predictors of RNFS. On univariate analysis, factors significantly associated with inferior RNFS were: SRS1 single fractionation vs. multiple fractionation (1-year RNFS 55.4% vs. 94.9%; $p = 0.049$),

heterogeneous or cystic lesion morphology at SRS1 vs. homogeneous (1-year RNFS 51.6% vs. 91.4%; $p = 0.022$), SRS1–SRS2 interval ≤ 12 months vs > 12 months (1-year RNFS 96.0% vs. 63.1%; $p = 0.003$) and values above the median for SRS1 BED₃ ($p = 0.021$), for SRS1 EQD₂(3) ($p = 0.028$), for SRS2 BED₁₀ ($p = 0.007$), for SRS2 BED₃ ($p = 0.022$), for SRS2 EQD₂(10) ($p = 0.007$), for SRS2 EQD₂(3) ($p = 0.022$), for cumulative BED₁₀ ($p = 0.027$), for cumulative BED₃ ($p = 0.044$), for cumulative EQD₂(10) ($p = 0.027$), for cumulative EQD₂(3) ($p = 0.015$). Sex, age, KPS, GPA, tumor histology, lesion location, cavity vs. intact lesion, GTV/PTV diameter and volume at both SRS1 and SRS2, brain dose–volume parameters (V5–V25), systemic therapy, and fractionation (single vs. multiple at SRS2) were not significantly associated with RNFS (all $p > 0.05$).

SRS1–SRS2 Interval and Its Relationship with Dose and Radionecrosis

The median SRS1–SRS2 interval was 11 months (range, 3–43 months). Although an interval of ≤ 12 months was associated with significantly lower RN risk compared with intervals > 12 months (1-year RNFS 96.0% vs. 63.1%; $p = 0.003$), this relationship was confounded by a significant difference in prescribed SRS2 doses between the two groups. Patients with shorter intervals (≤ 12 months) received significantly lower SRS2 EQD₂(10) doses (median 30.5 Gy; range, 23.3–42.75 Gy) than those with longer intervals (median 40 Gy; range, 28–50 Gy; Mann–Whitney U = 674.0, $p < 0.001$). The SRS1–SRS2 interval was not associated with LPFS ($p = 0.961$). (Fig. 2)

Dosimetric Thresholds for Radionecrosis Risk

ROC curve analysis was performed for the four dose parameters that were significant on univariate analysis for RN. Optimal thresholds were identified using the Youden index. SRS2 EQD₂(10) ≥ 33.6 Gy predicted RN with 80% sensitivity and 63% specificity (AUC 0.780, 95% CI 0.625–0.934; $p = 0.006$). Cumulative (SRS1 + SRS2) EQD₂(10) ≥ 75 Gy showed 80% sensitivity and 67% specificity (AUC 0.764, 95% CI 0.598–0.930; $p = 0.017$). SRS2 BED₃ ≥ 83.7 Gy demonstrated 80% sensitivity and 61% specificity (AUC 0.785, 95% CI 0.634–0.935; $p = 0.005$). Cumulative BED₃ ≥ 177 Gy yielded 80% sensitivity and 65% specificity (AUC 0.791, 95% CI 0.643–0.938; $p = 0.004$). These thresholds are summarized in Table 2.

Table 2

ROC-derived dosimetric thresholds for radionecrosis risk and their association with local control.

Parameter	Threshold	Sensitivity	Specificity	AUC	95% CI	p-value
SRS2 EQD ₂ (10)	33.6 Gy	80%	63%	0.780	0.625–0.934	0.006*
Cumulative EQD ₂ (10)	75 Gy	80%	67%	0.764	0.598–0.930	0.017*
SRS2 BED ₃	83.7 Gy	80%	61%	0.785	0.634–0.935	0.005*
Cumulative BED ₃	177 Gy	80%	65%	0.791	0.643–0.938	0.004*

AUC, area under the ROC curve; BED₃, biologically equivalent dose with $\alpha/\beta = 3$ Gy; cumulative, SRS1 + SRS2 values; EQD₂(10), equivalent dose in 2-Gy fractions with $\alpha/\beta = 10$ Gy. *Statistically significant ($p < 0.05$).

Kaplan–Meier analysis confirmed that patients receiving doses above versus below each threshold had significantly inferior RNFS. For SRS2 EQD₂(10) > 33.6 Gy, the 1- and 2-year RNFS rates were 63.8% and 53.2%, compared with 91.3% and 91.3% for those at or below the threshold ($p = 0.007$; Fig. 3a). For cumulative EQD₂(10) > 75 Gy, the 1- and 2-year RNFS rates were 63.2% and 52.7%, versus 91.4% and 91.4% ($p = 0.006$; Fig. 3b). For SRS2 BED₃ > 83.7 Gy, the 1- and 2-year rates were 65.8% and 56.4% versus 90.9% and 90.9% ($p = 0.013$; Fig. 3c). For cumulative BED₃ > 177 Gy, rates were 65.2% and 55.9% versus 91.0% and 91.0% ($p = 0.013$; Fig. 3d). Critically, none of these dosimetric thresholds was significantly associated with LPFS (all $p > 0.05$), indicating that dose escalation beyond these limits increases RN risk without a corresponding local control benefit.

Multivariable Analysis

On multivariable Cox regression analysis, none of the variables significant on univariate analysis—including SRS1 Dmax, SRS1 DS-GPA, prior brain SRS history and symptomatic status at SRS2—retained independent significance for LPFS (all $p > 0.05$). For RNFS, the variables entered the multivariable model were lesion morphology at SRS1 (homogeneous vs. heterogeneous/cystic), SRS1 fractionation (single vs. multiple), SRS1–SRS2 interval (≤ 12 vs. >12 months), and SRS2 EQD₂(10). None of these reached statistical significance as independent predictors (all $p > 0.05$), likely reflecting collinearity between interval duration and SRS2 dose, and limited statistical power given the total of 10 RN events.

DISCUSSION

In this retrospective analysis of 40 patients with 59 locally recurrent brain metastases treated with repeat SRS, we observed a one-year LPFS rate of 57.5% and a median local control duration of 27 months, with an overall RN rate of 20% at one year. These results are broadly consistent with the

published reSRS literature, which reports one-year local control rates of 60–89% and RN rates of 8–37% and support reSRS as an effective and feasible salvage option in appropriately selected patients^{10–32}.

A defining methodological feature of our cohort is the exclusion of patients with prior WBRT history. The role of WBRT has been narrowed to patients with widely disseminated intracranial disease and most patients now receive SRS-based treatment. Our study provides outcome data that are directly applicable to this contemporary patient population. Among the published reSRS series those by Hall (2025)¹⁰, Noguchi (2025)³², Kowalchuk (2022)¹¹, Kim (2018)¹⁶, and Minniti (2016)¹² share a similarly WBRT-naïve design.

Our one-year lesion-level LPFS of 57.5% lies at the lower boundary of the published range. Several factors likely contribute to this finding. 87.5% of all local recurrence events occurred within the first year of follow-up, resulting in an early decline of the LPFS curve. A conservative recurrence definition of us aligned with RANO-BM criteria—favoring classification of ambiguous lesions as recurrence—may underestimate LC. Differences in recurrence definition are likely a major source of the wide variation in reported LC rates across reSRS series. McKay for example applied volumetric increase thresholds of 200% for small and 25% for larger lesions (reported one-year LPFS 79%)¹⁷, while Minniti used sequential imaging enlargement as the sole criterion (one-year LPFS 70%)¹², and Koffer incorporated multiparametric MRI data (one-year LPFS 61%)¹⁵.

We did not identify tumor volume or diameter as a predictor of local control. This is in contrast with several prior series in which larger GTV/PTV was independently associated with inferior local control after reSRS. Kowalchuk reported a hazard ratio of 3.31 for GTV > 1 cm³, while Koiso (> 10 cm³), Koffer (> 4 cm³), and Kim (4 ml or 10 ml) identified volume-based thresholds for inferior control^{15,16,25}. However, Noguchi and Minniti did not show a relation between LC and volume/diameter in the multivariable analyses of their studies^{12,32}.

One of the most clinically relevant findings of our study was the identification of exploratory dosimetric thresholds associated with an increased risk of RN without an apparent improvement in local control. Although these thresholds should be interpreted cautiously given the limited number of RN events, they may provide useful preliminary guidance for treatment planning and future prospective validation studies. ROC analysis identified four biologically derived dose parameters predictive of RN: SRS2 EQD₂(10) ≥ 33.6 Gy, cumulative EQD₂(10) ≥ 75 Gy, SRS2 BED₃ ≥ 83.7 Gy, and cumulative BED₃ ≥ 177 Gy. Significantly lower RNFS at both 1 and 2-years for patients exceeding each threshold, with no corresponding improvement in LPFS (all $p > 0.05$) was seen. Translating these thresholds to common fractionation schemes, SRS2 regimens such as 5×5 Gy, 4×6 Gy, and 3×7 appear to remain within the identified safety margins. By contrast, single-fraction SRS2 at 15 Gy yields a BED₃ of 90 Gy, already exceeding the 83.7 Gy BED₃ threshold. These findings favor hypofractionated SRS over single-fraction delivery in the reSRS setting, particularly when SRS1 was also delivered at biologically higher doses.

An unexpected finding was the inverse association between SRS1–SRS2 interval and RN risk: patients with recurrence within 12 months after SRS1 had a one-year RN rate of only 4%, compared with 36.9% in those who recurred beyond 12 months ($p = 0.03$). A similar counterintuitive association was reported by Sneed, who observed increasing symptomatic necrosis rates with longer intervals (3%, 3%, 13%, and 19% for intervals of < 6 months, 6–11.9 months, 1–1.9 years, and ≥ 2 years, respectively)²³. On further analysis, we found that patients with shorter intervals received significantly lower SRS2 EQD₂(10) doses (median 30.5 Gy) compared with those with longer intervals (median 40 Gy; $p < 0.001$). This dose-related confounding likely explains the apparent association between treatment interval and RN: clinicians prescribed lower salvage doses for early recurrences, whereas longer disease-free intervals appeared to support greater confidence in dose escalation. Accordingly, interval duration should be interpreted together with prescribed dose rather than as an isolated predictor of RN risk.

Our RN rate of 20% at one year (symptomatic rate 13.5%) is consistent with the expected increase in necrosis risk following reSRS compared with first-line SRS. Hall reported a one-year RN rate of 15.6% after reSRS versus 3% after initial SRS¹⁰, while Noguchi reported 20.6% versus 5.7%, respectively³². Importantly, all but one symptomatic case in our cohort were manageable with conservative measures or short-course corticosteroids; ISRS grade 4 radiation necrosis requiring surgical intervention was observed in one patient. The favorable toxicity profile in our series likely reflects the predominantly hypofractionated approach, the exclusion of WBRT-exposed patients, and adherence to cumulative dose constraints.

Several limitations of this study warrant consideration. The retrospective design and relatively small sample size (40 patients and 59 lesions) limit statistical power and increase the risk of both type I and type II errors. Only 10 RN events were observed, restricting the robustness of multivariable and ROC-based analyses. Therefore, the proposed dosimetric thresholds should be considered hypothesis-generating rather than definitive clinical constraints. In addition, lesion-level analyses were performed without adjustment for potential within-patient clustering, which may have influenced variance estimates. The heterogeneity of treatment platforms (Gamma Knife, CyberKnife, and linac-based SRS), fractionation schedules, and dosimetric planning approaches reflects real-world practice but introduces additional variability. The inclusion of both intact metastases and surgical cavities may have contributed further heterogeneity. Finally, the absence of routine advanced imaging and the challenge of differentiating recurrence from RN without pathological confirmation represent important limitations of this study.

CONCLUSIONS

In conclusion, repeat SRS is an effective and well-tolerated salvage treatment for locally recurrent brain metastases after initial SRS, with median local control of 27 months and an acceptable toxicity profile. Our data suggest that biologically equivalent dose thresholds may be associated with a lower risk of radionecrosis without compromising local control. However, these findings should be regarded as

exploratory and require validation in larger multi-institutional cohorts before being incorporated into routine clinical practice.

Abbreviations

- **AE**

Adverse event

- **AUC**

Area under the curve

- **BED**

Biologically effective dose

- **CI**

Confidence interval

- **CT**

Computed tomography

- **CTCAE**

Common Terminology Criteria for Adverse Events

- **Dmax**

Maximum dose

- **DS-GPA**

Diagnosis-specific graded prognostic assessment

- **EQD2**

Equivalent dose in 2-Gy fractions

- **GI**

Gradient index

- **GTV**

Gross tumor volume

- **HI**

Homogeneity index

- **iDMFS**

Intracranial distant metastasis-free survival

- **IORT**

Intraoperative radiotherapy

- **IRB**

Institutional review board

- **ISRS**

International Stereotactic Radiosurgery Society

- **KPS**

Karnofsky Performance Status

- **LC**

Local control

- **LITT**

Laser interstitial thermal therapy

- **LPFS**

Local progression-free survival

- **MRI**

Magnetic resonance imaging

- **nCI**

New Paddick conformity index

- **OS**

Overall survival

- **PET**

Positron emission tomography

- **PIV**

Prescription isodose volume

- **PTV**

Planning target volume

- **RANO-BM**

Response Assessment in Neuro-Oncology Brain Metastases

- **RCC**

Renal cell carcinoma

- **RN**

Radiation necrosis

- **RNFS**

Radiation necrosis-free survival

- **ROC**

Receiver operating characteristic

- **SRS**

Stereotactic radiosurgery

- **SRS1**

Initial stereotactic radiosurgery

- **SRS2**

Repeat stereotactic radiosurgery

- **TV_PIV**

Target volume covered by the prescription isodose volume

- **WBRT**

Whole-brain radiotherapy

Declarations

Ethics approval and consent to participate: This study was approved by the Acibadem University Medical Research Ethics Committee (ATADEK) at its meeting on October 17, 2024 (meeting no. 2024/16; decision no. 2024-16/633). The requirement for informed consent to participate was waived by the Acibadem University Medical Research Ethics Committee (ATADEK). The study was conducted in accordance with the Declaration of Helsinki and all applicable guidelines and regulations.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: C.A.: Conceptualization, methodology, data collection, formal analysis, and writing – original draft. G.U.: Data collection, clinical interpretation, and writing – review and editing. E.T.: Data collection, clinical interpretation, and writing – review and editing. A.A.: Data collection, and writing – review and editing. Z.O.: Treatment planning data collection and dosimetric analysis. B.A.: Supervision, and writing – review and editing. M.S.: Clinical interpretation and writing – review and editing. E.O.: Data collection, clinical interpretation, supervision and writing – review and editing. U.A.: Data collection, clinical interpretation, conceptualization, supervision, and writing – review and editing. All authors reviewed and approved the final manuscript.

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Figures

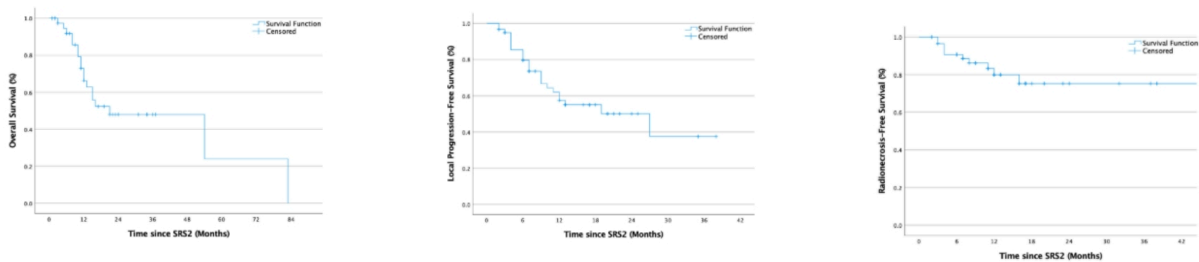


Figure 1

Kaplan–Meier curve: a. Overall survival b. Local progression-free survival c. Radionecrosis- free survival from SRS2.

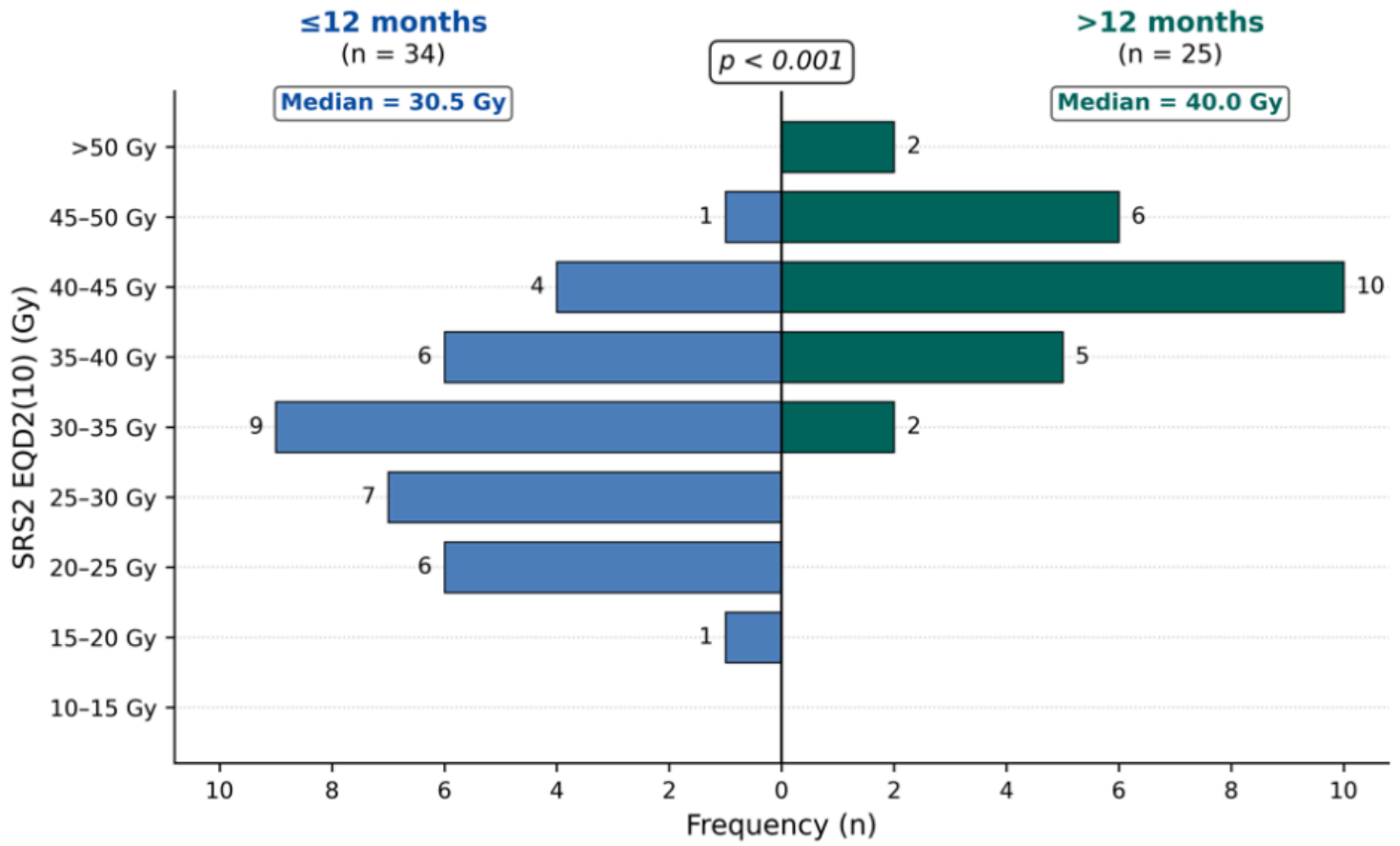


Figure 2

Distribution of SRS2 EQD₂(10) by SRS1-SRS2 Interval. Relationship between SRS1–SRS2 interval and prescribed SRS2 EQD₂(10) dose. Compared with patients retreated within 12 months, those retreated after >12 months received substantially higher SRS2 EQD₂(10) doses (median 40.0 Gy vs. 30.5 Gy, $p<0.001$)

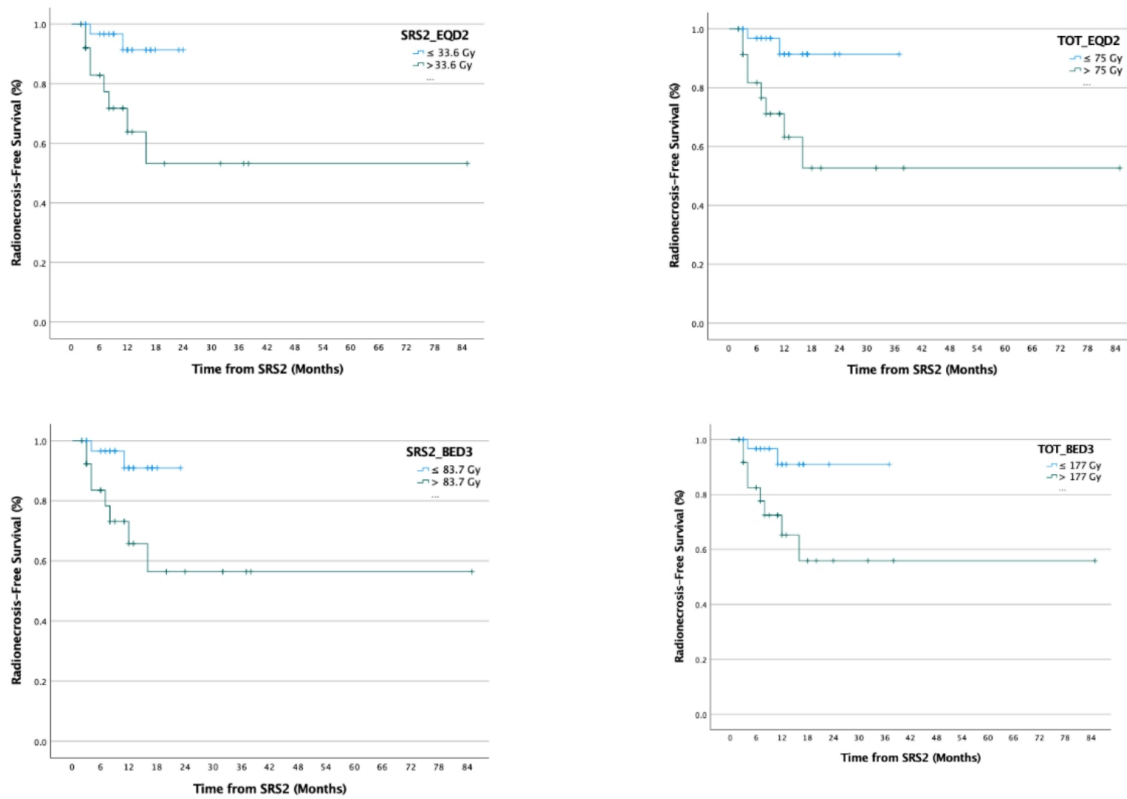


Figure 3

a. KM curve: RNFS by SRS2 EQD₂(10) threshold (33.6 Gy). b. KM curve: RN-free survival by cumulative EQD₂(10) threshold (75 Gy). c. KM curve: RN-free survival by SRS2 BED₃ threshold (83.7 Gy). d. KM curve: RN-free survival by cumulative BED₃ threshold (177 Gy).