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Deferring Whole-Brain Radiotherapy with Stereotactic Radiosurgery for Brain Metastases: A Prospective Cohort Study

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Abstract

Background: Whole-brain radiotherapy (WBRT) provides intracranial disease control but is associated with neurocognitive toxicity. Following stereotactic radiosurgery (SRS), selected intracranial recurrences may be managed with further focal treatment rather than immediate WBRT. We evaluated recurrence patterns, salvage treatment, and subsequent WBRT use in a prospective SRS/stereotactic radiotherapy (SRT) cohort.

Methods: Adults with brain metastases treated under a prospective institutional SRS/SRT protocol were included. Of 298 patients, 269 had received neither prior WBRT nor WBRT as part of index treatment and formed the primary cohort. Intracranial recurrence, salvage-treatment sequence, and radiation necrosis (RN)

were recorded. Cumulative incidence of salvage WBRT and overall RN was estimated with death as a competing event; WBRT-free survival, defined as time to salvage WBRT or death, was estimated using Kaplan–Meier analysis.

Results: Median follow-up was 12.8 months. Intracranial recurrence occurred in 110 of 269 patients (40.9%). Repeat SRS/SRT was first salvage in 47 patients, of whom six subsequently received WBRT. Overall, 34 patients (12.6%) received salvage WBRT. WBRT was selected as first salvage in 30.8%, 10.4%, and 38.8% of patients with isolated in-field, isolated out-of-field, and combined recurrence, respectively ($p = 0.005$). With death as a competing event, cumulative incidence of salvage WBRT was 3.1%, 8.3%, and 13.2% at 6, 12, and 24 months. Subsequent WBRT incidence after repeat SRS/SRT was 9.5% at 6 months and 12.1% at 12 months. Median WBRT-free survival was 14.6 months (95% CI, 11.7–17.4). Symptomatic RN occurred in 21 patients (7.8%); the 24-month cumulative incidence of overall RN was 10.2%.

Conclusions: Following initial SRS/SRT, intracranial tumour control was observed in 59.1% of patients, and 87.4% remained free from WBRT at their last recorded follow-up. Among selected patients receiving repeat SRS/SRT as first salvage, 87.2% (41/47) had no subsequent WBRT during available follow-up. These findings support continued focal intracranial management in selected patients, with potential neurocognitive benefits from limiting WBRT-associated toxicity.

Keywords: Brain metastases; stereotactic radiosurgery; whole-brain radiotherapy; salvage treatment; radiation necrosis

Background

Brain metastases are a frequent cause of neurological morbidity in patients with cancer. Improvements in systemic therapy and magnetic resonance imaging have increased the number of patients considered for focal intracranial treatment. Stereotactic radiosurgery (SRS) provides local control while limiting irradiation of uninvolved brain and is now commonly used for patients with a limited number of brain metastases and selected patients with more extensive intracranial disease.

Whole-brain radiotherapy (WBRT) improves intracranial control, but its neurocognitive effects remain a concern when prolonged disease control is achievable with focal treatment and improvements in modern systemic therapy. In a randomized trial, adding WBRT to SRS increased cognitive deterioration at 3 months from 63.5% to 91.7%, without improving overall survival.[1] Neuroprotective strategies have reduced this burden: memantine lowered the estimated probability of cognitive failure at 24 weeks from 64.9% to 53.8%,[2]

while hippocampal avoidance during WBRT plus memantine reduced executive-function deterioration at 4 months from 40.4% to 23.3%.[3] Although these advances have improved cognitive outcomes, they have not eliminated treatment-associated deterioration, providing a rationale for deferring WBRT in appropriately selected patients whose intracranial disease remains amenable to focal therapy.

When WBRT is omitted initially, close MRI surveillance is required because intracranial recurrence remains common. However, recurrence after SRS does not necessarily require immediate WBRT. Patients with limited intracranial progression may remain suitable for further focal treatment. In a retrospective series reported by Shultz et al., only 19 of 95 patients treated with multiple courses of SRS ultimately received WBRT. [4]

Prospective evidence for this approach remains limited. In the randomized phase II CYBER-SPACE trial, patients with 1–10 brain metastases underwent SRS followed by regular MRI surveillance, with repeat SRS permitted for new lesions. Freedom from a protocol-defined indication for WBRT at 12 months was 77.1%.[5] However, the patterns of intracranial recurrence, sequence of salvage treatment, and actual use of WBRT following initial SRS have not been well described in prospective cohorts.

The present study evaluated a prospective cohort of patients with brain metastases treated with SRS/SRT without prior WBRT. We examined intracranial recurrence patterns, the use and sequencing of salvage treatment, and the cumulative incidence of salvage WBRT. Radiation necrosis was assessed as a treatment-related outcome.

Methods

Study Design and Patient Population

This prospective observational cohort study was conducted at the Department of Radiation Oncology, Amrita Institute of Medical Sciences, Kochi, under an institutional protocol (AIMSIRB:2020-071; CTRI No. REF/2022/01/050237). Adult patients with brain metastases treated with stereotactic radiosurgery or stereotactic radiotherapy (SRS/SRT) were prospectively included between July 2017 and June 2026. Written informed consent was obtained from all participants.

This analysis expands our previously published prospective institutional SRS cohort and focuses on salvage-treatment sequencing and WBRT outcomes.[6]

The institutional cohort comprised 298 patients. For the present analysis, 26 patients with prior whole-brain radiotherapy (WBRT) and three receiving concurrent WBRT with a stereotactic boost were excluded, leaving

269 patients in the primary analysis cohort. Of these, 228 received upfront SRS/SRT and 41 received postoperative stereotactic treatment.

SRS/SRT Technique

Treatment was delivered using robotic stereotactic radiosurgery (*CyberKnife M6*). Patients underwent contrast-enhanced computed tomography (CT) simulation, with magnetic resonance imaging fused with the planning CT for target delineation. A planning target volume (PTV) margin of 2–3 mm was applied according to institutional practice and proximity to organs at risk.

Prescription doses ranged from 12 to 30 Gy delivered in 1–5 fractions. Dose and fractionation were individualized according to lesion size, location, clinical setting, and proximity to critical structures.

Follow-up and Assessment of Intracranial Recurrence

Patients underwent clinical and radiological surveillance following SRS/SRT. Contrast-enhanced MRI of the brain was performed at 3-month intervals during the first year and at 6-month intervals thereafter in patients with controlled intracranial disease.

The pattern of the first documented intracranial recurrence was classified according to its relationship to the previously treated field. In-field recurrence was defined as recurrence occurring within the previously treated PTV. Recurrence outside the prior PTV was classified as out-of-field recurrence. Patients with both in-field and out-of-field recurrence were classified as having combined recurrence.

Subsequent intracranial treatments, including repeat SRS/SRT, WBRT, and surgery, were recorded. Choice of salvage treatment was individualized according to the number and volume of recurrent metastases, prior intracranial treatment, performance status, extracranial disease status, expected survival, and technical feasibility of further SRS/SRT. For patients receiving repeat stereotactic treatment, the interval from index SRS/SRT to the first repeat SRS/SRT was calculated. Treatment sequencing was additionally assessed to identify patients in whom repeat SRS/SRT constituted the first intracranial salvage treatment and to determine whether WBRT was subsequently required.

Radiation Necrosis

Radiation necrosis was diagnosed on the basis of combined clinical and radiological assessment during follow-up, incorporating serial MRI findings and multidisciplinary clinical review where required. Advanced imaging such as perfusion MRI or MR spectroscopy were used selectively when the diagnosis remained uncertain. Events were recorded over the entire course of intracranial stereotactic treatment, including after subsequent

repeat SRS/SRT where applicable. Symptomatic status and treatment for radiation necrosis were recorded where applicable. Time to radiation necrosis was calculated from the date of index SRS/SRT to the documented diagnosis of radiation necrosis.

Study Endpoints

The primary outcome of the present analysis was the use of salvage WBRT after index SRS/SRT. Salvage WBRT was defined as any WBRT delivered after the index stereotactic treatment. The cumulative incidence of salvage WBRT was estimated at 6, 12, and 24 months, with death before WBRT treated as a competing event.

WBRT-free survival was evaluated as a secondary endpoint and was defined as the interval from index SRS/SRT to either salvage WBRT or death, whichever occurred first. Patients alive without WBRT were censored at their last documented follow-up.

Other secondary outcomes included the incidence and pattern of first intracranial recurrence, initial salvage treatment, the number of repeat SRS/SRT treatments among patients receiving repeat SRS/SRT as first salvage, and the interval from index SRS/SRT to the first repeat treatment. Subsequent WBRT use in this subgroup was also assessed, together with the association between first recurrence pattern and selection of WBRT as initial salvage. Radiation necrosis and its cumulative incidence were evaluated. Overall survival from index SRS/SRT to death from any cause was also calculated.

Follow-up was calculated from the date of index SRS/SRT to the date of death or last documented clinical assessment.

Statistical Analysis

Continuous variables were summarized using medians and interquartile ranges (IQRs), while categorical variables were expressed as frequencies and percentages. The association between the pattern of first intracranial recurrence and selection of WBRT as the first salvage treatment was assessed using chi-square test. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

Because death precludes the subsequent administration of salvage WBRT, the probability of receiving WBRT was estimated using a competing-risk framework. Salvage WBRT was considered the event of interest, death without prior WBRT was treated as the competing event, and patients alive without WBRT at last follow-up were censored. The non-parametric cumulative incidence function was the primary time-to-event analysis and was used to estimate the probability of salvage WBRT at 6, 12, and 24 months.

For comparison with the competing-risk analysis, time to salvage WBRT was analyzed in the entire primary cohort (n=269) from index SRS/SRT using the conventional Kaplan–Meier method, with salvage WBRT as the event. Deaths without prior WBRT were censored at the time of death and patients alive without WBRT were censored at their last follow-up.

WBRT-free survival was estimated using the Kaplan–Meier method, with either salvage WBRT or death considered an event, whichever occurred first. Patients alive without WBRT were censored at their last documented follow-up. Time from index SRS/SRT to salvage WBRT was summarized as the median and IQR among patients who received salvage WBRT. Overall survival was estimated using the Kaplan–Meier method, with death from any cause as the event and surviving patients censored at last follow-up.

Radiation necrosis was analysed using an analogous competing-risk approach. Radiation necrosis was considered the event of interest, death before development of radiation necrosis was treated as the competing event, and patients alive without radiation necrosis at last follow-up were censored. Cumulative incidence of radiation necrosis was estimated at 6, 12, and 24 months.

Among patients who received repeat SRS/SRT as their first salvage treatment, time to subsequent WBRT was measured from the date of the first repeat SRS/SRT treatment. Subsequent WBRT was treated as the event of interest, death before WBRT as a competing event, and patients alive without subsequent WBRT were censored at last follow-up.

Descriptive statistics, categorical comparisons, and Kaplan–Meier analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA), and competing-risk cumulative incidence functions were estimated using cmprsk version 2.2.12 in R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Use of generative artificial intelligence

ChatGPT (OpenAI) was used to assist with manuscript wording, language refinement, and framing. All statistical analyses were independently performed and verified by the authors. The authors reviewed the final text and take full responsibility for the manuscript's content.

Results

Patient and Treatment Characteristics

The primary analysis cohort comprised 269 WBRT-naïve patients. Median age was 59 years (IQR, 50–68) and median Karnofsky Performance Status (KPS) was 80 (IQR, 80–90). Lung cancer was the most common primary malignancy, accounting for 40.9% of the cohort, followed by breast cancer in 29.7%.

Solitary brain metastasis was present in 145 patients (53.9%), while 83 (30.9%) had 2–3 metastases, 34 (12.6%) had 4–5 metastases, and 7 (2.6%) had more than five metastases. Upfront SRS/SRT was delivered in 228 patients (84.8%), while 41 (15.2%) received postoperative treatment. Median observed follow-up was 12.8 months (IQR, 5.7–21.1). Baseline and treatment characteristics are summarized in **Table 1**.

At data cutoff on 25 August 2026, 37 patients (13.8%) were lost to follow-up and were censored at their last documented assessment.

Intracranial Recurrence and Salvage Treatment

Intracranial recurrence occurred in 110 of 269 patients (40.9%). Among patients with recurrence, 13 (11.8%) developed isolated in-field failure, 48 (43.6%) isolated out-of-field failure, and 49 (44.5%) combined in-field and out-of-field recurrence.

Among the 110 patients with intracranial recurrence, 76 (69.1%) received intracranial salvage treatment. First-salvage treatments: 47 patients (42.7%) underwent repeat SRS/SRT, 28 (25.5%) received WBRT, and one (0.9%) underwent salvage surgery; 34 (30.9%) received no further intracranial treatment. Reasons for no salvage included death before treatment could be delivered, poor performance status, or transition to best supportive care. Three additional patients underwent repeat SRS/SRT after initially receiving salvage WBRT. The cohort and salvage-treatment pathways are summarized in Figure 1.

Among the 47 patients receiving repeat SRS/SRT as first salvage, the median time from index SRS/SRT to the first repeat stereotactic treatment was 8.7 months (IQR, 6.8–13.5). Forty patients (85.1%) received repeat SRS/SRT once, four (8.5%) received repeat SRS/SRT twice, and three (6.4%) received repeat SRS/SRT thrice. Six subsequently received WBRT, while 41 had no documented subsequent WBRT during available follow-up. With death treated as a competing event, the cumulative incidence of subsequent WBRT after repeat SRS/SRT was 9.5% at 6 months, 12.1% at 12 months, and 15.0% at 24 months (Figure 2).

First Recurrence Pattern and Initial Salvage Treatment

At the first intracranial recurrence, WBRT was selected as the initial salvage treatment in 4 of 13 patients (30.8%) with isolated in-field recurrence, 5 of 48 (10.4%) with isolated out-of-field recurrence, and 19 of 49 (38.8%) with combined recurrence. The association between first recurrence pattern and selection of WBRT as the initial salvage treatment was statistically significant (Pearson $\chi^2 = 10.50$, $p = 0.005$) **(Table 2)**.

Salvage WBRT Over Time

During follow-up, 34 patients received salvage WBRT, while 149 died without having received WBRT. The low cumulative incidence of salvage WBRT should therefore be interpreted in the context of substantial competing mortality.

By conventional Kaplan–Meier estimation of time to salvage WBRT, with deaths without WBRT censored, the estimated freedom from salvage WBRT was 96.4% at 6 months, 89.2% at 12 months, and 79.5% at 24 months. The median time to salvage WBRT was not reached in the full primary cohort (n=269; 34 WBRT events). Among the 34 patients who received salvage WBRT, the observed median interval from index SRS/SRT to WBRT was 11.2 months (IQR, 6.8–16.1) **(Table 3)**.

When death without prior WBRT was treated as a competing event, cumulative incidence of salvage WBRT was 3.1% at 6 months, 8.3% at 12 months, and 13.2% at 24 months (**Table 3; Figure 3**).

When salvage WBRT or death was considered an event, Kaplan–Meier WBRT-free survival was 78.2% at 6 months, 57.4% at 12 months, and 28.4% at 24 months. Median WBRT-free survival was 14.6 months (95% CI, 11.7–17.4) (**Table 3; Figure 4**). There were 183 composite events, comprising 34 salvage WBRT events and 149 deaths before WBRT; 86 patients were censored.

For overall survival, 171 deaths occurred among the 269 patients. Median overall survival was 17.5 months (95% CI 14.6 – 20.4), with 12- and 24-month survival estimates of 63.5% and 33.1%, respectively (**Table 3**).

Radiation Necrosis

Symptomatic radiation necrosis was observed in 21 of 269 patients (7.8%). Overall, 25 patients (9.3%) developed radiation necrosis, including four asymptomatic patients. Median time from index SRS/SRT to diagnosis of radiation necrosis was 5.9 months (IQR, 3.3–10.6).

Management included corticosteroids alone in 12 patients, corticosteroids plus hyperbaric oxygen therapy in eight, and surgery in one; four patients required no specific intervention (**Table 4**).

With death before radiation necrosis treated as a competing event, cumulative incidence of radiation necrosis was 5.1% at 6 months, 8.1% at 12 months, and 10.2% at 24 months (**Table 3; Figure 5**).

Discussion

In the primary cohort of 269 patients treated with an SRS/SRT-based strategy without prior WBRT, intracranial recurrence occurred in 110 patients (40.9%), and 235 (87.4%) did not receive salvage WBRT during available follow-up. In this same cohort, the competing-risk cumulative incidence of salvage WBRT was 8.3% at 12 months and 13.2% at 24 months. Repeat SRS/SRT was the first salvage treatment in 47 patients (17.5% of the whole cohort; 42.7% of patients with intracranial recurrence). Six (12.8%) subsequently received WBRT, while 41 (87.2%) had no subsequent WBRT. In this selected subgroup, the competing-risk cumulative incidence of subsequent WBRT was 12.1% at 12 months from the first repeat SRS/SRT treatment.

When survival and avoidance of WBRT were considered together, median WBRT-free survival was 14.6 months (95% CI, 11.7–17.4 months), with estimates of 78.2%, 57.4%, and 28.4% at 6, 12, and 24 months, respectively. This endpoint represents the duration for which patients remained both alive and free from salvage WBRT, complementing the competing-risk analysis of actual WBRT utilization. Importantly, intracranial recurrence or repeat SRS/SRT did not itself constitute an event. WBRT-free survival therefore captures continued WBRT-sparing management, including further focal treatment, rather than freedom from intracranial progression.

The relatively low use of salvage WBRT in the present cohort is consistent with contemporary SRS series. In a multi-institutional study of 2089 patients undergoing initial SRS, Hughes et al. reported 2-year cumulative incidences of salvage WBRT of 12%, 15%, and 16% among patients with 1, 2–4, and 5–15 brain metastases, respectively.[7] Our 24-month cumulative incidence of 13.2% falls within this range. Similarly, Shultz et al. reported that only 19 of 95 patients (20%) receiving multiple courses of SRS ultimately underwent WBRT.[4] More recently, the CYBER-SPACE trial demonstrated that repeated SRS combined with MRI surveillance could maintain 77.1% freedom from a protocol-defined indication for WBRT at 12 months.[5] Direct numerical comparison with CYBER-SPACE is limited because its endpoint was a predefined indication for WBRT rather than actual administration of salvage WBRT, but both studies support the same broader treatment concept: recurrent intracranial disease can frequently be managed without immediate transition to WBRT.

The sequence of salvage treatment provides further insight into this strategy. Among 47 patients in whom repeat SRS/SRT represented the first salvage intervention, 41 (87.2%) did not subsequently receive WBRT

during available follow-up. This observation is clinically relevant because it examines what happens after the decision to pursue focal salvage rather than simply reporting the proportion of the overall cohort receiving repeat SRS. Patients offered repeat SRS are likely to have limited intracranial disease burden, lesions suitable for further focal therapy, adequate performance status, and sufficient expected survival to benefit from another stereotactic procedure. Our results support repeat SRS/SRT as an option for extending focal management beyond the initial treatment course in appropriately selected patients.

The pattern of first intracranial recurrence was associated with the initial salvage treatment selected. WBRT was used as first salvage in 38.8% of patients with combined in-field and out-of-field recurrence, compared with 30.8% of those with isolated in-field recurrence and 10.4% with isolated out-of-field recurrence ($p = 0.005$). Isolated out-of-field recurrence was least likely to prompt immediate WBRT, suggesting that the development of new metastases outside previously treated targets could often be managed without an immediate transition to whole-brain treatment. Conversely, combined local and distant failure more frequently led directly to WBRT, potentially reflecting greater intracranial disease burden. These findings describe treatment-selection patterns; recurrence pattern was not established as an independent predictor.

The clinical relevance of WBRT deferral lies partly in reducing exposure of uninvolved brain to treatment-associated neurocognitive toxicity. Randomized data have established that adding conventional WBRT to SRS improves intracranial control but increases cognitive deterioration without improving overall survival in patients with limited brain metastases. Brown et al. reported cognitive deterioration at 3 months in 91.7% of evaluable patients receiving SRS plus WBRT compared with 63.5% after SRS alone, with better preservation of quality of life in the SRS-alone group.[1] In the placebo arm of the RTOG 0614 trial reported by Brown et al., patients receiving WBRT had an estimated 64.9% probability of cognitive failure at 24 weeks, compared with 53.8% in the memantine arm.[2] A recent phase III trial in 103 patients with breast cancer and 1–5 brain metastases reported no significant difference in overall or progression-free survival between upfront WBRT and SRS, while cognitive decline was lower with SRS.[8] Because that trial evaluated initial treatment in a disease-specific population rather than salvage after index SRS/SRT, it provides contextual rather than directly comparable evidence for the present WBRT-deferral strategy. Modern WBRT has become less neurotoxic: in NRG CC001, hippocampal-avoidance WBRT with memantine significantly reduced the risk of cognitive failure compared with conventional WBRT plus memantine.[3] Nevertheless, mitigation is not equivalent to elimination of cognitive effects, and avoiding or delaying WBRT remains clinically meaningful when

intracranial disease can be managed safely with focal therapy. Repeat SRS/SRT may extend this WBRT-sparing approach to selected patients who develop further intracranial disease.

The feasibility of an SRS-centered strategy must also be considered alongside treatment toxicity. Radiation necrosis occurred in 9.3% of the cohort, with a competing-risk cumulative incidence of 10.2% at 24 months. Symptomatic radiation necrosis affected 21 of 269 patients (7.8%). Most were managed conservatively; one patient required surgical intervention. These rates are broadly comparable with previously reported SRS experience, although comparisons are complicated by differences in whether radiation necrosis is reported per patient or per lesion, whether asymptomatic radiographic changes are included, and the methods used for diagnosis. The long-term update of the prospective JLGK0901 cohort reported cumulative incidences of SRS-associated complications of approximately 10–11% at 24 months across patients with 1–10 metastases, although this endpoint was broader than radiation necrosis alone.[9] CYBER-SPACE reported grade 3 radiation necrosis in 4.6% of its overall cohort.[5] Other large SRS series have reported radiographic radiation necrosis rates in the range of approximately 5–10%, with risk influenced by factors including lesion size, dose-volume parameters, previous irradiation, and systemic therapy.[10] The radiation-necrosis estimates in the present study reflect the eligible cohort as a whole and should not be interpreted as the risk attributable specifically to repeat SRS/SRT.

Competing mortality was substantial, with 149 of 269 patients dying without prior salvage WBRT. In a separate Kaplan–Meier analysis of time to salvage WBRT that censored these deaths, the estimated 24-month probability of WBRT was 20.5%, compared with the competing-risk cumulative incidence of 13.2%. The latter more appropriately estimates the observed probability of salvage WBRT in this population. This death-censored analysis is distinct from the composite WBRT-free survival analysis, in which either salvage WBRT or death was counted as an event.

Several limitations should be acknowledged. This was a single-institution, non-randomized study, and the decision to use repeat SRS or WBRT was based on clinical selection. The finding that 41 of 47 patients had no documented subsequent WBRT applies specifically to patients selected for focal salvage and does not establish superiority over other salvage approaches. The cohort included heterogeneous primary malignancies, systemic therapies, treatment volumes, and SRS/SRT fractionation schedules. Median observed follow-up was 12.8 months, limiting assessment of very late WBRT use and late radiation necrosis in long-term survivors. For subsequent WBRT after first-salvage repeat SRS/SRT, only three patients remained at risk at 24 months; the 15.0% estimate at this time point should therefore be interpreted cautiously. Finally, formal neurocognitive

and quality-of-life assessments were not incorporated; the potential cognitive benefit of WBRT deferral in this cohort therefore cannot be directly quantified.

Conclusions

Following initial SRS/SRT, intracranial tumour control was observed in 59.1% of patients, and 87.4% remained free from WBRT at their last recorded follow-up. Among selected patients receiving repeat SRS/SRT as first salvage, 87.2% (41/47) had no subsequent WBRT during available follow-up. These findings support continued focal intracranial management in selected patients, with potential neurocognitive benefits from limiting exposure to WBRT-associated toxicity. Careful patient selection and surveillance for radiation necrosis remain important.

Abbreviations

CT: Computed tomography

CTRI: Clinical Trials Registry–India

HBOT: Hyperbaric oxygen therapy

IQR: Interquartile range

KM: Kaplan–Meier

KPS: Karnofsky Performance Status

MRI: Magnetic resonance imaging

PTV: Planning target volume

RN: Radiation necrosis

SRS: Stereotactic radiosurgery

SRT: Stereotactic radiotherapy

WBRT: Whole-brain radiotherapy

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Amrita Institute of Medical Sciences (AIMSIRB:2020-071) and was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Clinical Trial number

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient confidentiality and privacy considerations but are available from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

A.M. updated and curated the departmental cohort database, performed the statistical analyses, interpreted the results, prepared the figures and tables, and drafted and revised the manuscript. K.S. and A.S. assisted with the statistical analysis, interpretation of the results, and preparation and critical revision of the manuscript. D.D. contributed substantially to patient recruitment and clinical management, provided clinical resources, assisted with interpretation of the findings, and critically reviewed the manuscript. H.S. and V.K. contributed to data acquisition and curation and reviewed the manuscript. A.E.H. contributed to radiotherapy planning and treatment-delivery methodology and provided technical validation. R.K. contributed to radiological assessment and validation of intracranial recurrence patterns. A.R., P.K.U., H.M.N., and P.N. contributed to the clinical management of patients, interpretation of the findings, and critical review of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for the integrity of the work.

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Tables and Figures

Table 1: Baseline and treatment characteristics of the primary analysis cohort

Characteristic	**Overall cohort (n=269)**
Patient characteristics	
Age, years, median (IQR)	59 (50–68)
Karnofsky Performance Status, median (IQR)	80 (80–90)
Sex, n (%)	
Male	124 (46.1%)
Female	145 (53.9%)
Primary malignancy, n (%)	
Lung	110 (40.9%)
Breast	80 (29.7%)
Other (includes Gynecological, genitourinary, gastrointestinal, renal malignancies)	79 (29.4%)
Intracranial disease burden, n (%)	
Solitary metastasis	145 (53.9%)
2–3 metastases	83 (30.9%)
4–5 metastases	34 (12.6%)
>5 metastases	7 (2.6%)
Treatment setting, n (%)	
Upfront SRS/SRT	228 (84.8%)

Characteristic	Overall cohort (n=269)
Postoperative SRS/SRT	41 (15.2%)
Follow-up, months, median (IQR)	12.8 (5.7–21.1)

Table 2: Intracranial recurrence, salvage treatment, and relationship between recurrence pattern and salvage WBRT

2A: Recurrence and salvage outcomes

Outcome	n (%)
Intracranial recurrence	110/269 (40.9%)
Failure pattern among recurrent patients (n=110)	
Isolated in-field recurrence	13 (11.8%)
Isolated out-of-field recurrence	48 (43.6%)
Combined in-field and out-of-field recurrence	49 (44.5%)
Any intracranial salvage treatment	76/110 (69.1%)
Repeat SRS/SRT as first salvage	47/110 (42.7%)
WBRT as first salvage	28/110 (25.5%)
Surgery as first salvage	1/110 (0.9%)
No salvage treatment after recurrence	34/110 (30.9%)
Repeat SRS/SRT as first salvage (n=47)	
One repeat SRS/SRT	40/47 (85.1%)
Two repeat SRS/SRT	4/47 (8.5%)
Three repeat SRS/SRT	3/47 (6.4%)
Time to first repeat SRS/SRT, months, median (IQR)	8.7 (6.8–13.5)
No subsequent WBRT after repeat SRS/SRT as first salvage	41/47 (87.2%)
Subsequent WBRT after repeat SRS/SRT as first salvage	6/47 (12.8%)

2B: WBRT as first salvage according to intracranial recurrence pattern

Recurrence pattern	WBRT not selected as first salvage, n (%)	WBRT selected as first salvage, n (%)	Total
Isolated in-field	9 (69.2%)	4 (30.8%)	13
Isolated out-of-field	43 (89.6%)	5 (10.4%)	48

Recurrence pattern	WBRT not selected as first salvage, n (%)	WBRT selected as first salvage, n (%)	Total
Combined	30 (61.2%)	19 (38.8%)	49
Total	82 (74.5%)	28 (25.5%)	110

Pearson $\chi^2 = 10.50$; $p = 0.005$

Table 3: Time-dependent salvage WBRT, WBRT-free survival, overall survival and radiation necrosis outcomes

3A: Time-point estimates

Outcome	6 months	12 months	24 months
Conventional KM freedom from salvage WBRT [a]	96.4%	89.2%	79.5%
Cumulative incidence of salvage WBRT [b]	3.1%	8.3%	13.2%
WBRT-free survival (WBRT or death) [c]	78.2%	57.4%	28.4%
Cumulative incidence of subsequent WBRT after first-salvage repeat SRS/SRT [d]	9.5%	12.1%	15.0%
Cumulative incidence of radiation necrosis [e]	5.1%	8.1%	10.2%
Overall survival [f]	80.5%	63.5%	33.1%

[a] Kaplan–Meier estimate of freedom from salvage WBRT, with deaths without prior WBRT censored.

[b] Death without prior WBRT treated as a competing event.

[c] Kaplan–Meier estimate with either salvage WBRT or death considered an event.

[d] Time measured from the first repeat SRS/SRT treatment, with death before subsequent WBRT treated as a competing event.

[e] Death before radiation necrosis treated as a competing event.

[f] Kaplan–Meier estimate with death from any cause considered an event.

3B: Median time-to-event summaries

Outcome and analysis population	Median, months
Time to salvage WBRT (n=269; Kaplan–Meier, deaths censored)	Not reached
Observed interval to WBRT among recipients only (n=34)	11.2 (IQR, 6.8–16.1)
WBRT-free survival (n=269; WBRT or death)	14.6 (95% CI, 11.7–17.4)
Overall survival (n=269)	17.5 (95% CI 14.6 – 20.4)

Table 4: Clinical presentation and management of radiation necrosis

Characteristic	n (%)
Radiation necrosis	25/269 (9.3%)
Median time to diagnosis, months (IQR)	5.9 (3.3–10.6)
Clinical presentation	
Symptomatic	21/269 (7.8%)
Asymptomatic	4/269 (1.5%)
Management	
No specific intervention	4/25 (16.0%)
Corticosteroids alone	12/25 (48.0%)
Corticosteroids + Hyperbaric Oxygen Therapy	8/25 (32.0%)
Surgery	1/25 (4.0%)

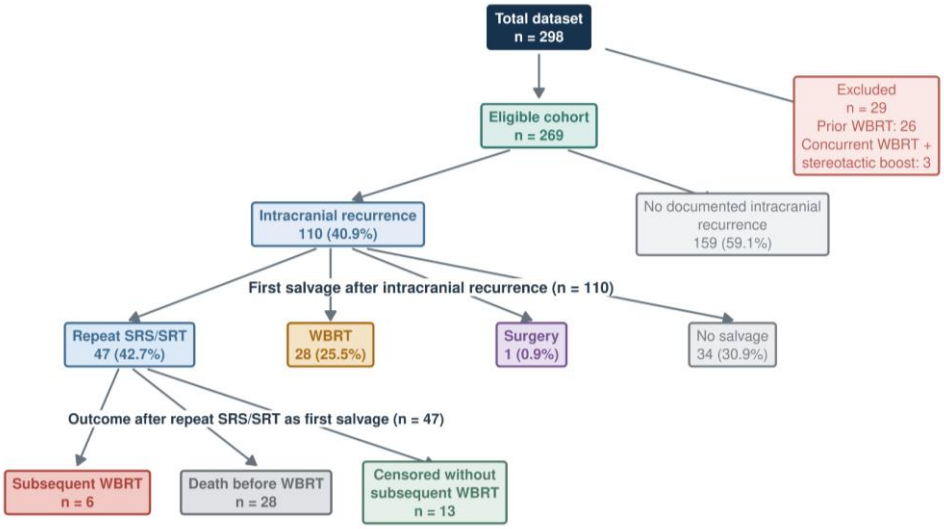


Figure 1: Patient cohort and intracranial salvage pathways.

Flow diagram showing cohort selection, intracranial recurrence, first salvage treatment, and outcomes after repeat SRS/SRT as first salvage. Death before subsequent WBRT was treated as a competing event, and patients without subsequent WBRT or death were censored.

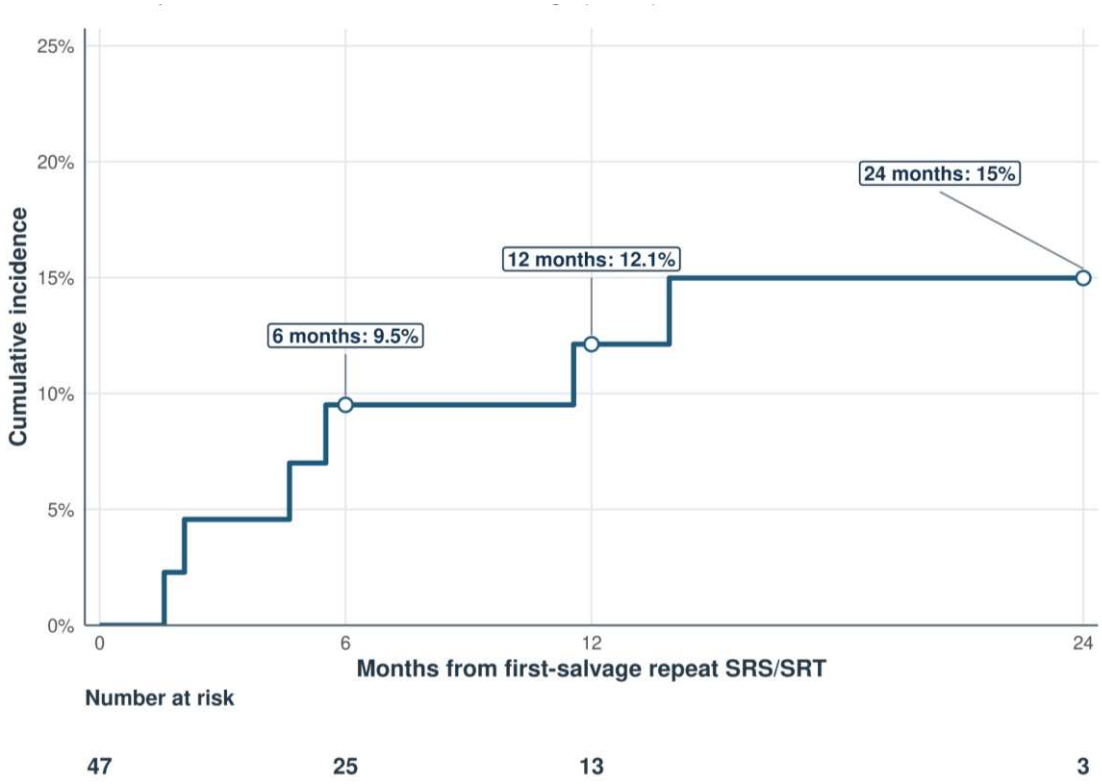


Figure 2: Cumulative incidence of subsequent WBRT after repeat SRS/SRT as first salvage.

Time was measured from the first-salvage repeat SRS/SRT treatment. Subsequent WBRT was the event of interest, death before WBRT was the competing event, and remaining patients were censored. Cumulative incidence was 9.5% at 6 months, 12.1% at 12 months, and 15.0% at 24 months.

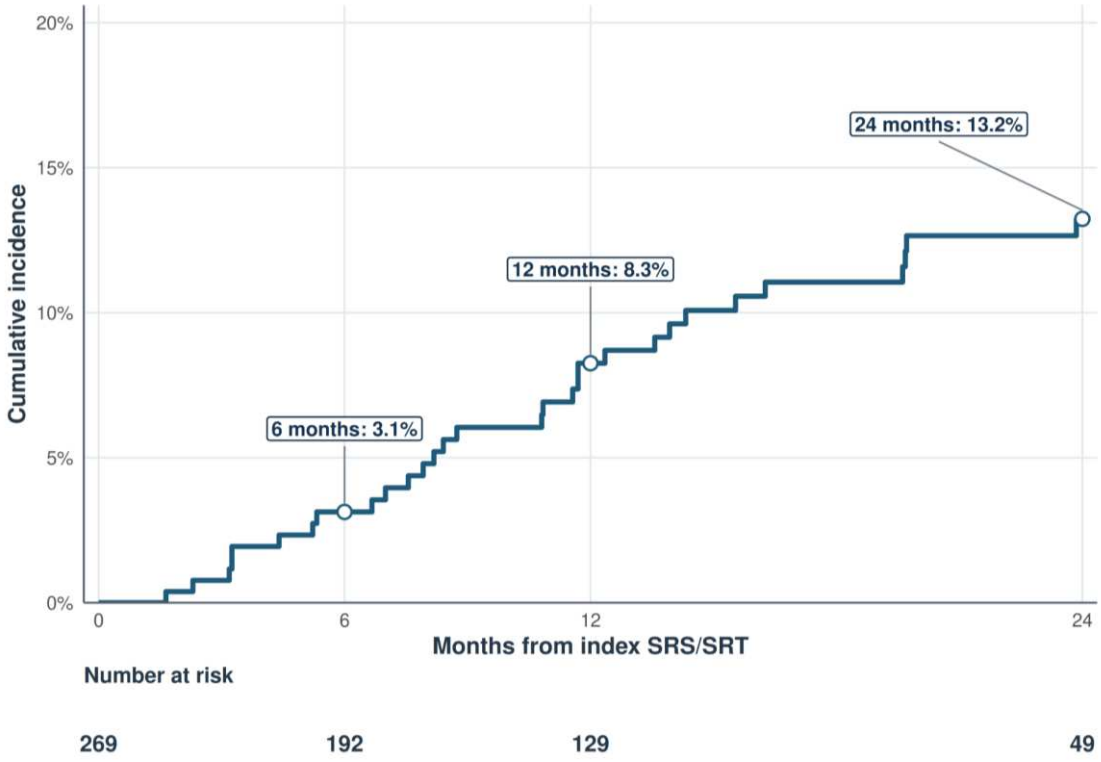


Figure 3: Cumulative incidence of salvage whole-brain radiotherapy following index SRS/SRT.

Non-parametric cumulative incidence function for salvage WBRT with death without prior WBRT treated as a competing event. The cumulative incidence of salvage WBRT was 3.1% at 6 months, 8.3% at 12 months, and 13.2% at 24 months.

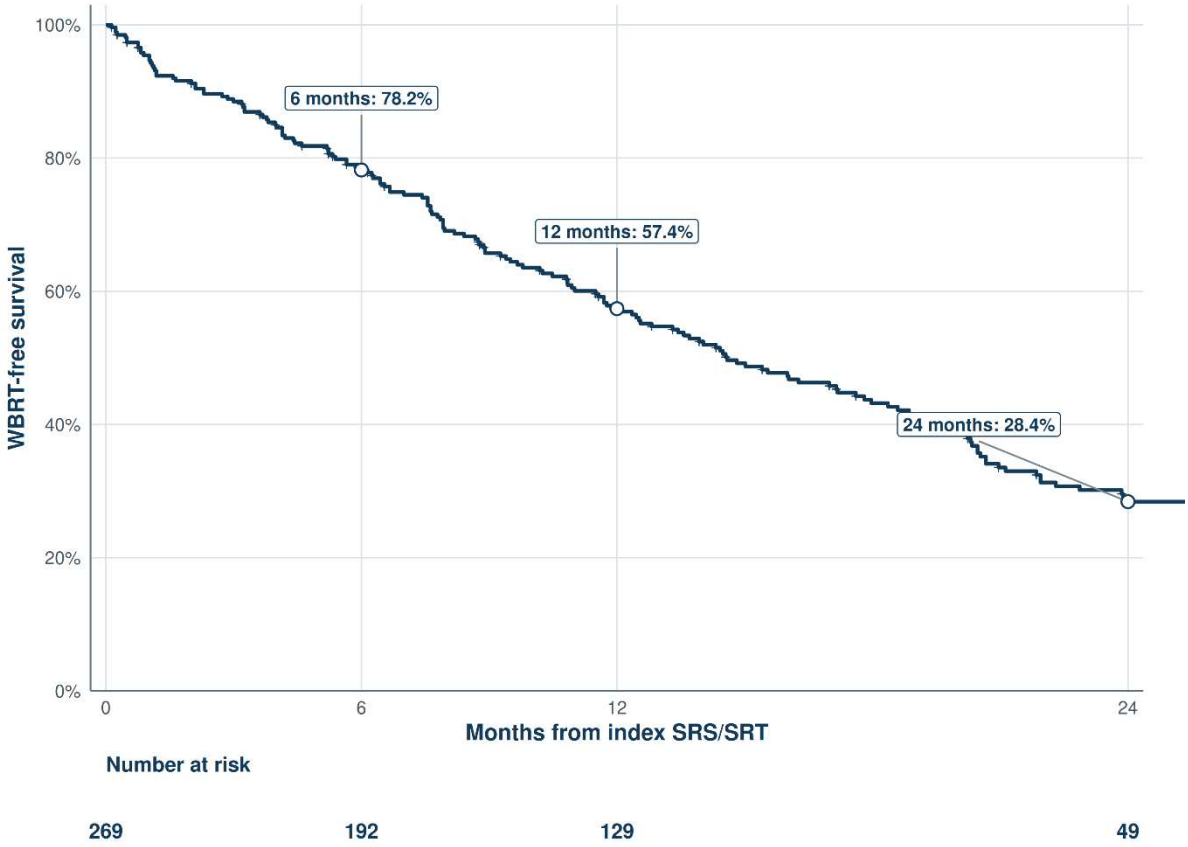
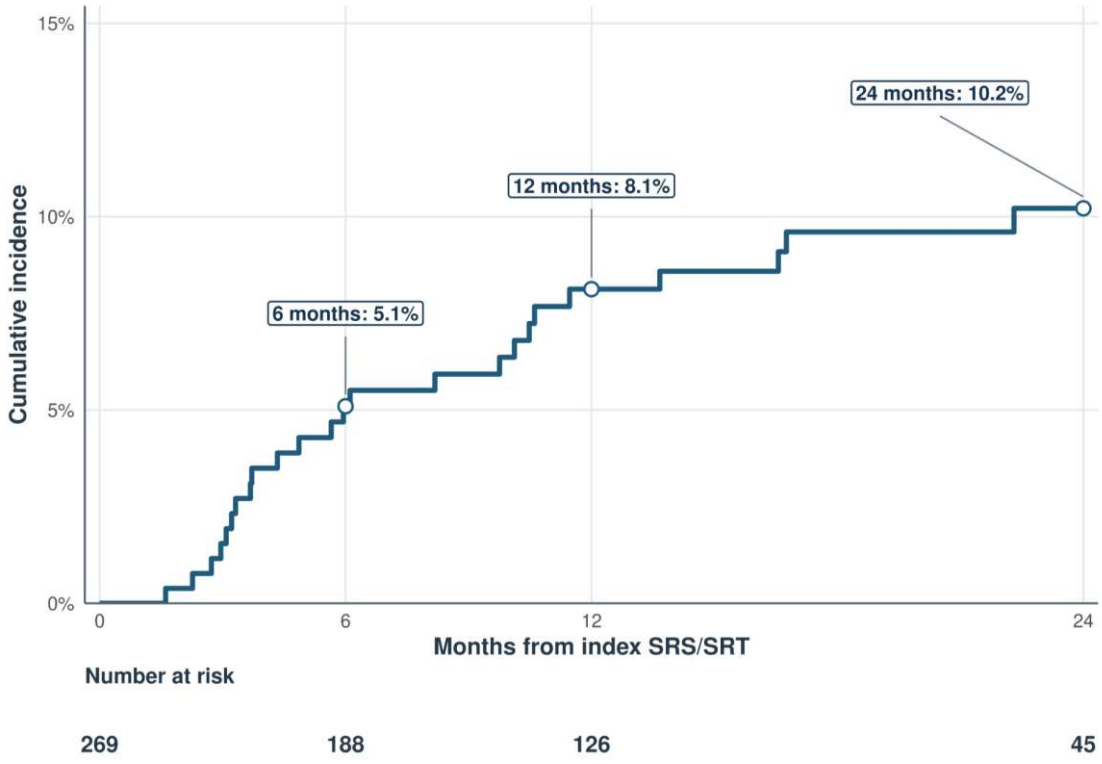


Figure 4: WBRT-free survival following index SRS/SRT.

Kaplan–Meier estimate of WBRT-free survival (composite endpoint of salvage WBRT or death), defined as the interval from index SRS/SRT to either event, whichever occurred first. Patients alive without WBRT were censored at last documented follow-up.



436

437 **Figure 5: Cumulative incidence of radiation necrosis following index SRS/SRT.**

438 Non-parametric cumulative incidence function for radiation necrosis with death before radiation necrosis

439 treated as a competing event. The cumulative incidence of radiation necrosis was 5.1% at 6 months, 8.1% at

440 12 months, and 10.2% at 24 months.