



Tumor Cavity Stereotactic Radiosurgery for Resected Brain Metastases

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Authors' contributions

This work was carried out in collaboration among all authors. Authors YB, US and ET designed the study, wrote the protocol and the first draft of the manuscript. Authors AK, SS, DS, NKD and BP managed the analyses of the study. Authors EYA, YB and BP managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Stereotactic radiosurgery (SRS) has been utilized broadly for brain metastases not only for intact ones but as well as of late for the postoperative cavity of metastases after surgery, due to the advantages of SRS to preserve neurocognitive functions, maintain local control and prescribe the treatment in a short time frame. Randomized trials have proven the safety and efficacy of cavity SRS compared to observation. As WBRT offers no survival advantage in comparison to SRS and frequent monitorization with brain MRIs for early salvage upon failure, there has been a revolution in clinical approach for patients with limited intact brain metastases to treat with SRS only and omit WBRT. Likewise, the postoperative cavity SRS for brain metastases has gained a growing reputation. In this review, we summarize the proof for evidence-based optimization in the postoperative setting of the surgically removed brain metastases.

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1. INTRODUCTION

Brain metastasis (BM) occurring in 20–40% of all patients with solid tumors are directly related to morbidity and mortality, with practically half of them being single metastasis [1-3]. The most frequent solid malignancies developing BM are lung cancer (36-64 %), breast cancer (15-25%), and malignant melanoma (5-20%) [3]. The mainstay of management for single BM has been surgical resection which has been documented to improve survival outcomes when combined with whole-brain radiotherapy (WBRT) in comparison to WBRT alone [4,5]. However, it is crucial to individualize the decisive intervention by valuing the patient and tumor-related factors.

The best-fit treatment strategy for BM is ideally determined by accounting for the patient's age, performance status, pathology of the primary tumor, extracranial disease status, individual or total BM volume, and the number of BMs, BM-related symptoms and location of the BMs [6-9]. Surgical resection alone was considered to render poor rates of durable local control, and consequently, postoperative WBRT was bolstered to decrease the risk of local recurrences within the resection cavity and elsewhere in the brain [3,10,11]. However, WBRT studies have documented a close link with declined cognition [12-15]. Hence, the feasibility of the routine use of WBRT after BM resection has been questioned particularly in patients presenting with quantitatively limited BMs [16,17]. One notable back-up option was postoperative stereotactic radiosurgery (PO-SRS) to the resection cavity/cavities of single or multiple BMs rather than the significantly toxic WBRT [18-20]. In this unique situation, PO-SRS following modern dedicated microsurgical resection of BMs sound to provide acceptable local control rates of 70-93% compared to the results of the surgery followed by WBRT [21,22].

This review article intends to address the current status of emerging PO-SRS to provide practical decision guidance for the clinicians in the modern management of the BMs.

2. DATA COLLECTION METHODOLOGY

As this was a comprehensive literature review on the PO-SRS applications and outcomes, we tried to identify all accessible studies on the subject from January 1998 to April 2020. For this

purpose the search terms 'postoperative radiosurgery' or 'postoperative tumor cavity' or 'brain metastases' were used to search PubMed. Additionally, the previous reports on WBRT, neurosurgical tumor resection, preoperative cranial radiosurgery were reviewed to select related literature to provide a well-balanced discussion on the subject.

2.1 Whole-brain Radiotherapy Following Surgical Resection

Historically, WBRT was the favored treatment approach for reducing the risk of local and elsewhere new lesions in the brain [1,3,10,21-23]. WBRT was tested in two randomized phase III trials with or without surgical resection for single BM and the addition of surgical resection unveiled an improvement of overall survival times [4,5]. Omitting WBRT after surgical resection was studied in a randomized phase III trial by Patchell et al. inferred that the omission of WBRT let 46% local recurrence and overall 70% intracranial failures [10]. Postoperative WBRT has attained justification in case of limited BMs and WBRT by reducing the local recurrence rate to 14%, defining the microscopic disease to be addressed in the surgical bed, but with caution in interpreting the trial related to a high local recurrence rate of 46%, much higher than the rates for SRS alone, and with the evaluation of the extent of BMs lacking the contrast (double gadolinium or gadobenate dimeglumine) enhanced thin-slice volumetric magnetic resonance images possibly missing some small lesions [10]. On the other hand, omitting WBRT and using SRS alone in case of 1 to 3-4 intact BMs was addressed in four randomized phase III trials comparing SRS and SRS plus WBRT, with results establishing that overall survival was not diminished with SRS alone but the risk for intracranial failures was significantly increased opposed to SRS plus WBRT regimes [12,15, 24,25].

The randomized trial from the European Organization for Research and Treatment of Cancer (EORTC) 22952-26001 investigated the role of adjuvant WBRT after either surgery or SRS of 1 to 3 BMs from solid tumors [25]. Recruiting 359 patients treated with SRS (n=199) or complete surgery (n=160) and randomly to one of adjuvant WBRT (30 Gy in 10 fractions) or observation (OBS) arms uncovered that the WBRT efficiently reduced the 2-year relapse

rates both at initial sites (surgery: 59% to 27%, $P < 0.001$; SRS: 31% to 19%, $P = 0.040$) and at elsewhere (surgery: 42% to 23%, $P = 0.008$; SRS: 48% to 33%, $P = 0.023$) in comparison to OBS arm. In spite of the fact that the WBRT offered a modest increase in progression-free survival results, the increased intracranial tumor control did not translate into an asset of prolonged survival times with functional independence or into a prolonged overall survival time (median overall survival; WBRT, 10.9 vs OBS, 10.7 months; $P > 0.05$). In a further analysis of EORTC 22952 data by Churilla et al, the authors assessed the impact of WBRT on survival outcomes for patients with the controlled extracranial disease or favorable prognoses, reckoning the extracranial progression as a time-dependent covariate and diagnosis-specific graded prognostic assessment (GPA) score in patients with primary non-small-cell lung cancers (NSCLC) [26]. The researchers could report no significant distinction in the model-based risk of death in the WBRT group before or after extracranial progression, while no noteworthy survival benefit to WBRT among 175 NSCLC patients with favorable or unfavorable GPA scores. Justifying with this evidence, the perspective of cancellation of WBRT after surgery or SRS seems to have emerged for patients with limited or controlled extracranial disease and 1 to 3 BMs [26].

Neurocognitive functions were proven to be fundamentally more regrettable with WBRT [15], and this long-term neurocognitive diminishment is turning out to be progressively more significant nowadays as the cancer patients live much longer than those reported in the historic series to a large extent due to the implementation of more compelling systemic therapies to the treatment algorithms of such patients. As the initial omission of WBRT has been shown to not negatively alter the distant brain relapse rates in an individual patient meta-analysis, where SRS alone favored survival for the patients under 50 years of age, SRS alone might be granted as the standard of care for 1 to 3-4 BMs [26-28]. The neurocognitive functions of cancer patients had been influenced by several factors such as BMs, BM volume, location of the BM (particularly the hippocampi), intra- and/or extra-cranial progression, paraneoplastic effects, medications, chemotherapy, hormone therapy, surgery, accidental exposure to ionizing radiation, prior neurologic disease, and the utilization of WBRT [29]. One of the most striking critics against the utilization of WBRT is its strong demonstration as

a negative factor on neurocognitive functions and quality of life measures. The very first randomized study on this topic published by Chang et al. enrolled patients with 1 to 3 newly diagnosed BMs to receive SRS plus WBRT versus SRS alone while measuring the pattern of changes in the learning and memory functions of them [12]. Chang et al objectively measured the significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months; following 58 recruited patients ($n=30$ for SRS alone versus $n=28$ for SRS plus WBRT), the trial was terminated earlier than the planned data due to the demonstration of patients receiving SRS plus WBRT had progressive decrement in learning and memory functions at 4 months in comparison to receiving SRS alone group, with the respective mean probabilities of decline 52% versus 24% [12]. This level I proof didn't just proclaim SRS in addition to WBRT causing a decrease in learning and memory capacities, yet additionally noticed that the freedom from CNS recurrence at 1 year was 73% with SRS plus WBRT while only 27% with SRS alone ($p=0.0003$) too, uncovering a space to consider SRS alone to better preserve learning and memory batteries with the caution to monitor closely for CNS recurrences [12].

2.2 SRS Following Surgical Resection

The role of PO-SRS alone has first been established in Memorial Sloan-Kettering Cancer Center phase 2 trial by Brennan et al., reporting the first prospective study in 39 patients with 50 intra-parenchymal BMs treated by SRS following a median of 31 days after the surgery [30]. Local control was attained in 85% of all lesions with a median dose of 18 Gy (range: 15-22 Gy). The prognostic factors favoring an improved local control were identified as improved local control were identified to be the NSCLC histology, BM diameter < 3 cm, and deep parenchymal BM location; while the poorest local control was linked to BMs ≥ 3 cm with superficial dural/pial involvement (only 53.3% at 12 months). Brennan et al additionally remarked that infratentorial BMs following resection exhibited an essentially higher hazard for intracranial metastasis outside the treated volume as opposed to the supratentorial BMs [30].

The first randomized trial evaluating neurological outcomes (a decrease of the neurological score by ≥ 1 point or a worsening of the Mini-Mental test by at least 3 points, or neurological death) in

patients with resected single BMs, enrolling to PO-SRS (n= 29) of single fraction 15 Gy (or 5 × 5 Gy/fraction) versus WBRT (n= 30) of traditional 30 Gy given in 10 fractions was reported by Kepka and colleagues [31]. At a median follow-up of 29 months, the cumulative incidence of neurological/cognitive failure was more prevalent in the WBRT group at 6 months, and 2-year neurological death rates were 66% and 31% for PO-SRS versus WBRT arms, respectively. But OS was 10% versus 37% for PO-SRS versus WBRT arms, separately. Regrettably, this was an underpowered study to compare the clinical benefit of SRS against the WBRT. In another study, Berger et al. evaluated the cognitive functions of 12 patients with 1-2 BMs besides the quality of life (QOL; QLQ-30, QLQ-BN20) measures before and 3 months after the PO-SRS [32]. PO-SRS sounded a safe neuro-cognitive profile with preservation of nearly all quality of life parameters, indicating patients younger than 60 years benefit most and may even recover some cognitive functions within a few months after the treatment, namely the median global cognitive score, immediate verbal memory and the executive functions [32].

If WBRT would be on hold, the most desirable adjuvant treatment following surgical resection demanded to be addressed in patients with limited BMs. The phase III trial performed by Mahajan et al. analyzed 128 patients following complete surgical resection of at least one of 1 to 3 BMs being assigned to PO-SRS or observation alone arms [19]. Tumor cavities > 3 cm were found to be directly connected with worse local control, but the patterns of local failure based on the clinical target volumes were not detailed, while the larger the volume of the cavity the lower dose being prescribed in this study; 12 to 16 Gy was delivered according to the cavity volume. The local control rates at 6 and 12 months for PO-SRS versus observation arms were 83% and 72% versus 57% and 45%, respectively. However, the 1-year local control rate of 45% in the observation arm seemed to be lower than expected compared to that reported by Patchell et al. previously, while a couple of characteristics such as preoperative tumor size and the criteria to report local control (actuarial vs. crude rates) might be standardized to legitimize such comparisons. Mahajan et al could not demonstrate any meaningful diversity in rates of regional brain recurrence (58% vs. 67%), overall survival (17 vs. 17 months), or time to WBRT (16.1 vs. 15.2 months) endpoints between the two treatment cohorts.

The NCCTG N107C multicentric phase 3 trial was published by Brown et al. reporting 194 patients with 1 to 4 BMs randomized to receive either SRS (12–20 Gy/fraction for 1 resection cavity < 5.0 cm in maximum diameter) or WBRT (30 Gy, 3 Gy/fraction/day or 37.5 Gy, 2.5 Gy/fraction/day at discretion of treating center) after resection, while all unresected BMs received SRS in both arms [33]. As in Mahajan et al. study, larger the volume of the cavity lower the dose being prescribed (20 Gy <4.2 mL, 18 Gy for 4.2–7.9 mL, 17 Gy for 8.0–14.3 mL, 15 Gy for 14.4–19.9 mL, 14 Gy for 20.0–29.9 mL, 12 Gy ≥30.0 mL). Brown et al documented no significant median overall survival duration difference (11.5 months for SRS and 11.8 months for WBRT) between the two arms, while underlined better overall intracranial tumor control rates with WBRT at 6- (90% versus 74% for SRS) and 12-months (78.6% versus 54.7% for SRS), and better median surgical bed relapse-free survival with WBRT (7.7 versus 7.5 months for SRS); but declared significantly longer survival without cognitive decline by SRS in comparison to WBRT (cognitive decline at 6 months: SRS, 53.8% versus WBRT, 85.7%), as well as better physical well-being and quality of life in SRS arm. Central review for local recurrence decision was very important in N107C to rule out radiation necrosis (RN) or recurrence where 20% of the SRS group further received WBRT as salvage therapy [33].

2.3 Leptomeningeal Dissemination

A systematic review and meta-analysis by Lamba et al, based on 8 retrospective cohort studies including 646 patients who underwent PO-SRS (n= 238) or adjuvant WBRT (n= 408) revealed that 14 to 24 Gy PO-SRS might offer comparable survival, as well as similar local and distant recurrence rates compared to 30 to 37.5 Gy adjuvant WBRT delivered in 10 to 15 fractions, yet at the expense of an elevated risk of leptomeningeal dissemination (LMD) [34]. Hsieh et al. [35] reported the Cleveland Clinic experience of 212 patients (156 WBRT, 37 SRS, 19 intraoperative radiotherapy) on LMD [LMD risk with SRS alone: HR= 2.45] and Patel et al. [36] reported the Emory University experience of 132 patients with 141 resected metastases (36 WBRT, 96 SRS alone) (LMD risk with SRS alone: HR= 5.67), revealing an LMD incidence rate of 12% to 14% after PO-SRS alone. The pooled analysis of these two studies exhibited that the relative risk for increased LMD incidence was 2.99 following PO-SRS compared to the

adjuvant WBRT, with defining a relatively higher risk for the breast cancer originated BMs [34-36]. Atalar et al. [37] documented on LMD in their retrospective cohort of 165 patients with 175 resection cavities treated with PO- SRS without WBRT. The 1-year cumulative LMD incidence rate was 10% in this study, and confirming the results of the pooled results of the Hsieh et al. [35] and Patel et al. [36] breast cancer histology was accounted for to be the main factor associated with an increased risk of LMD in the univariate analysis, where 1-year cumulative incidences of LMD were 24% and 9% for breast- and non-breast cancer histologies (HR= 2.96). The rate of LMD sounds similar among treatment techniques and delivered machines; a retrospective Gamma Knife (GK) SRS series reported 96 BM resection cavities [non-small cell lung (43%), melanoma (14%), and breast (13%)] treated with a median dose of 16 Gy delivered to the 50% isodose line [38]. In this series, Ojerholm et al. reported a local failure rate of 18% and 1-year actuarial local control of 81%, while LMD developed in 12 cases (14%) bringing up to an association with breast histology and infratentorial cavities.

Prabhu et al. analyzed a total of 147 patients with LMD from 7 tertiary care centers and categorized the pattern of LMD as nodular (nLMD) or classical ("sugarcoating," cLMD) [39]. The authors have reported that being treated with WBRT was linked with a lower second LMD recurrence rate compared to focal RT (40% versus 68%; P=0.02), while nLMD was associated with longer median overall survival times than the cLMD counterparts (8.2 versus 3.3 months, P< 0.001). Interestingly, Prabhu et al emphasized that the pattern of initial LMD (nodular vs. classical) was significant on multivariable analysis for overall survival, but the type of salvage RT (WBRT versus focal) was not. Shi et al. recently presented the largest single-center PO-SRS series from Stanford University including 442 patients with 501 resected BMs, and also distinguished the cLMD and nLMD patterns [40]. They have pointed out that the overall incidence of LMD was 15.8% (53% cLMD, 46% nLMD), with cLMD being associated with shorter survival times than the nLMD (2.0 versus 11.2 months, P < 0.01) as well as a higher proportion of neurologic death (67% versus 41%, P = 0.02).

2.4 Radiation Necrosis

The retrospective series published a wide range of 1.5 to 18.5% radiographic radiation necrosis

(RN) rate following PO-SRS [22]. While WBRT in Patel's study [36] was the only significant prognostic factor for reduced elsewhere brain relapses in multivariate analysis, the incidence of radiographic leukoencephalopathy steeply increased with WBRT at 12 months (47 versus 7%; P = 0.001). On the other hand, the prerequisite for steroids after treatment was high in the SRS group in comparison to WBRT (27% versus 0%) [10,36]. Minniti et al. had analyzed the dosimetric parameters in plans of 106 patients with 310 BMs less than 3.5 cm who were treated with SRS as the primary treatment [41]. The investigators recorded overall neurological complications in 27 (13%) patients with RN being developed in 24% (symptomatic: 10% and asymptomatic: 14%) of the treated lesions. On multivariate analysis, V_{10} (volume receiving 10 Gy) through V_{16} was found to be the independent risk factor for RN, with V_{10} and V_{12} being the most predictive (P= 0.0001). Minniti et al. concluded a radionecrosis risk >10% if V_{12} >8.5 cm³, but when both V_{10} >12.6 cm³ and V_{12} >10.9 cm³ were evident the risk of RN was increasing up to 47%. Therefore, caution and hypofractionated stereotactic radiotherapy was advised by this Italian experience especially for lesions residing in or nearby the eloquent areas and if V_{12} of single fraction regimes are unacceptably high. Keller et al. retrospectively analyzed their hypofractionated stereotactic radiotherapy (3 × 7.7 Gy prescribed to the 70% isodose line) experience for resected BM cavities [42]. The RN rate was 18.5% after a median follow-up of 15 months for the 189 treated cavities, with RNs being symptomatic only in one-third of all cases. Keller et al noted only infra-tentorial location to be predictive of RN (HR= 2.97; P=0.0025) in multivariate analysis with V_{14} showing a trend approaching significance (P= 0.059).

Overall, the factors underlying the RN, particularly the symptomatic ones, following PO-SRS appeared to be obscure in the literature due to the broad variations in the diagnostic criteria, radiologic examination, and management approaches. Accordingly, further large-scale studies are justified to define the definite risk factors for RN development following the PO-SRS, which may serve valuably in the avoidance of this unpredictable yet severe toxicity of PO-SRS.

2.5 Timing of Stereotactic Radiotherapy

The promising and viable timing of PO-SRS for resected BMs has not been unveiled to date.

Postoperative edema-related increments in the tumor bed cavity size after the surgery may modify the target volume to remarkable degrees. On the other hand, postponing the PO-SRS past 3 weeks with the intention of significant tumor bed cavity contraction may provoke adverse consequences on the accurate targeting procedure balancing the patient's healing period [36]. Yuan et al. has published a critical review of the relationship between the tumor volume and the timing of PO-SRS by including seven studies that provided data on cavity dynamics after BM resection within the past 10 years [43]. The cavity volumes have typically reduced in a range of %43 to %58 in the following 1-month period from the surgery [43,44], while this reduction was noted to reach up to 84.8% when the interval to SRS has extended to 59 days [45]. Iorio-Morin et al. retrospectively analyzed the outcomes of 100 patients who underwent PO-SRS inconsiderate of the extent of curative resection or prior WBRT status. In the multivariate analysis, one of the independent risk factors for local recurrence was stated as the delay to start the PO-SRS > 3 weeks of surgical procedure [46]. Alghamdi et al explicitly remarked a necessary caveat when treating cavities in early interval <21 days after the surgery, as it may lead to irradiating more normal tissue especially in small tumors, in their series of 61 cavities in 59 patients [47]. Overall, the most recent international consensus recommended the delivery of the PO-SRS within the first 4 weeks of the postoperative period, if suitable [48].

2.6 Target Volume Delineation for Stereotactic Radiosurgery

Many retrospective GK- or LINAC-based PO-SRS series lacking a standard approach for the target volume delineation has been published to date. A retrospective LINAC series by Do et al. treating patients with 1 to 4 BMs with a dose of 15-18 Gy for single-fraction SRS and 22-27.5 Gy in 4 to 6 fractions for hypofractionated SRS, documented their target margins as an expansion over surgical cavity by 1 mm for rigid immobilization and 3-mm for mask immobilization and revealed a recurrence of only 13.3% (4/30) in the resection cavity [49]. In another retrospective single-institutional study, Bilger et al defined target volumes as the gross tumor volume (GTV) encompassing the residual tumor delineated on the T1-MRI, the clinical target volume (CTV) encompassing the surgical cavity plus 1-mm and the planning target volume (PTV) by addition of 2-mm to CTV, to deliver 30 Gy (5

Gy per day) after complete macroscopic resection and 35 Gy (5 Gy per day) after gross residual tumor and achieved an attractive local control rate with only 3.8% recurrences [50]. Choi et al. retrospectively studied the convenience of "no margin" or 2 mm margin for a postoperative cavity on local control and toxicity outcomes; and concluded a local control profit and increased toxicity with 2-mm cavity margin decreasing the 12-month cumulative incidence rates of local failure from 16% to 3%, and increasing the 12-month cumulative toxicity rates of from 3% to 8% [51].

The prospective NCCTG-N107C multicentric phase 3 trial refined the details as a 2-mm margin expansion around the CTV which was defined as the surgical cavity, while the surgical access tracts for deep lesions were not treated for deep lesions [33]. The local recurrence rates were lower than WBRT, but no additional information about the patterns of failure relative to the CTV was reported. Shi et al. in their retrospective Stanford University experience comprising 442 patients with 501 resected BMs argued that the majority of cavities (76%) were treated with a margin of 1- to 3-mm, with 65% of deep tumors (>1 cm from pia matter) having had the surgical corridor covered [40].

In this background, the consensus guideline of the delineation of the surgical cavity for PO-SRS was published by Soliman et al. which has been widely accepted in clinical practice [48]. The guideline consensus was generated by 10 international experts basing on the selected case contours of 6 patients of a wide variety of locations in the brain: supra- and infra-tentorial, deep and superficial, and dural or venous sinus contact; with a level of agreement of a mean sensitivity of 0.75 and specificity of 0.98 [48]. Simulation computerized tomography (CT) is recommended to be without routine contrast, while fusion with T1-weighted post gadolinium MRI and post-operative T2-FLAIR and postoperative T1 pre-gadolinium MRI phases was recommended for the optimal contouring procedure. Basics in CTV contouring were as follows: CTV should include the entire contrast-enhancing surgical cavity based on the T1 postgadolinium axial MRI excluding the edema; should include the entire surgical tract seen on post-operative CT/MRI; should include a 5-10 mm margin along the bone flap beyond the initial region of preoperative tumor contact if the tumor was in contact with the dura; could include a margin of 1 to 5 mm along the bone flap if the

tumor was not in contact with the dura; and could include 1 to 5 mm along the sinus if the tumor was in contact with a venous sinus (Table 1 and Fig. 1) [48]. These expert recommendations will ease to unify further clinical studies and practice, while calls validation in a prospective large-scale trial.

2.7 Optimal Dose for Stereotactic Radiosurgery

Optimal dose prescription for cavity SRS has been usually relied upon the size of the postsurgical cavities on MRI and planning CT scans. Therefore, the size-dependent established dose algorithm of the RTOG 90-05 trial for intact BMs has been extrapolated to the most PO-SRS cases [52]. Brennan et al. [30] published a phase 2 trial displaying maximum cavity size tailored SRS data prescribing 22 Gy for 2.0 cm; 18 Gy for 2.1-3.0 cm, and 15 Gy for 3.1-4.0 cm, and underlined the higher local failure rates at 12 months for cavity diameter ≥ 3 cm (39.1% versus 7.5% for < 3 cm). Besides, Mahajan et al. [19] compared the PO-SRS versus observation in their randomized trial and announced significantly decreased local 12-month control rate for the cavities ≥ 3 cm (58% versus 86% in < 3 cm). Additionally, Mahajan et al demonstrated an outstanding 100% local control rate of 100% for cavities ≤ 2.5 cm and ≤ 10 cc volumetrically and treated with a single fraction PO-SRS dose of 16 Gy. Brown et al. [33] prescribed higher cavity doses in NCCTG N107C, with more dose options per volume range (20 Gy for < 4.2 mL, 18 Gy for 4.2-7.9 mL, 17 Gy for 8.0-14.3 mL, 15 Gy for 14R 4-19.9 mL, 14 Gy for 20.0-29.9 mL, 12 Gy ≥ 30.0 mL).

Fractionated PO-SRS were also proposed to increase the probability of local control without sacrificing the RN risk. This PO-SRS option has gained popularity particularly for LINAC-based SRS applications mostly related to the flexibility of fractionation with LINACs than the GK machines. Bilger et al analyzed the single-center retrospective data of patients treated with 30 Gy (5 Gy per day) for grossly resected BMs and 35 Gy (5 Gy per day) PO-SRS for macroscopic residual disease, documenting only 2 out of 58 patients with local recurrences and the 12-month local control rate was 81.5% which was higher than the single-fraction PO-SRS results [50]. In another investigation, Traylor et al, showed that higher biologically equivalent dose (BED_{10}) was the most important factor to linking meningioma with longer local recurrence-free survival on

multivariate analysis [53]. Kumar et al. [54] treated 43 surgical beds of 39 consecutive patients with hypofractionated PO-SRS given in 3 or 5 fractions and documented well tolerance without any grade ≥ 3 toxicity and improved local control with $BED_{10} \geq 48$ (30 Gy in 5 fractions and 27 Gy in 3 fractions). With a median follow up of 226 days, the best local control with 5 fractions was by 30 Gy (93%) with only 1 local failure, while lower total dose in five fractions (i.e; 27.5 or 25 Gy) had a lower local control (70%). Likewise, the best local control with 3 fractions with a median follow up of 600 days was by 27 Gy (100%) which was decreased to 71% if dose was reduced to 24 Gy [54].

Garimall et al. recently documented Australian experience with 144 cavities treated in 134 patients [mostly malignant melanoma ($n=49$) and lung ($n=32$)] where 87% underwent gross total resection [55]. Median PTV was 28 cm³ (range: 2.4-149.2); and median EQD₂ [10] was 38.4 Gy (range 22.3-59.7) while 24 Gy in 3 fractions was the most common regimen in their series with limited toxicity of 7 (5%) patients experiencing grade ≥ 3 toxicities. Only 12 (9%) patients had local recurrence at median interval of 215 days (range: 4 - 594). In multivariate analysis, EQD₁₀ was associated with local failure; such that increased equivalent doses improved local control [HR = 0.79 and 95% CI 0.65-0.96, P = 0.0192]. Garimall et al. could not define any significance for primary histology, patient age, residual disease volume, PTV volume or location in their hypofractionated protocol. This Australian experience pointed out that hypofractionated PO-SRS with higher doses improved local control with low toxicity [55]. Kubler et al published their German experience on PO-SRS (single-fraction 16 Gy) and hypofractionated SRS (30 Gy in 3 fractions of 10 Gy) to tumor cavities with GK (N= 54 and CK, (N= 32) in two large centers [56], 54 cavities (66.7%) received hypofractionated SRS and 27 (33.3%) received single-fraction SRS. While local control was 83.3% at 1 year, there was no difference in overall survival, or local control between GK and CK treatments or single-fraction and hypofractionated PO-SRS. Mousli et al published the Belgian experience evaluating 70 patients treated with single and 3-5 fractionated PO-SRS with a marginal dose prescribed to the 70% isodose line (15-18 Gy for single, 23.1-26 Gy in 3-5 fractions), with cumulative local relapse incidences of 4% and 15% at 6- and 12-months, respectively [57]. Their univariate analysis displayed higher local recurrence with an initial volume > 7 cc (HR= 4.6;

P= 0.046) and a positive resection margins (HR= 3.6; P= 0.037). Symptomatic RN and LMD occurred in 7.1% and 12.9% of cases, while salvage WBRT was necessitated for 45.7% of patients with a median time to WBRT of 9.6 months. PO-SRS was an effective and well-tolerated treatment to control the postoperative BM recurrence risk without compromising survival outcomes. In the largest retrospective series to date, Shi et al. documented 7%, 9%, and 13% rates for local failure, severe adverse reactions, and LMD at 12 months, individually, in 442 patients with 501 resected BMs treated over

475 PO-SRS courses [40]. Most treatments were completed in 3 fractions with a median dose of 24 Gy. The 12-months local failure rates per PO-SRS fractions were: 4.1%, 22.2%, 6% and 16.7% for 1, 2, 3 and 5 fractions, respectively, with an ultimate requirement for WBRT rate of only 15%.

In this context, tailoring the PO-SRS based on the size of the BM cavity, location of the BM, tolerance of adjacent critical structures sounds reasonable, safe and effective with single fraction PO-SRS up to 2.5 cm cavities by a prescription

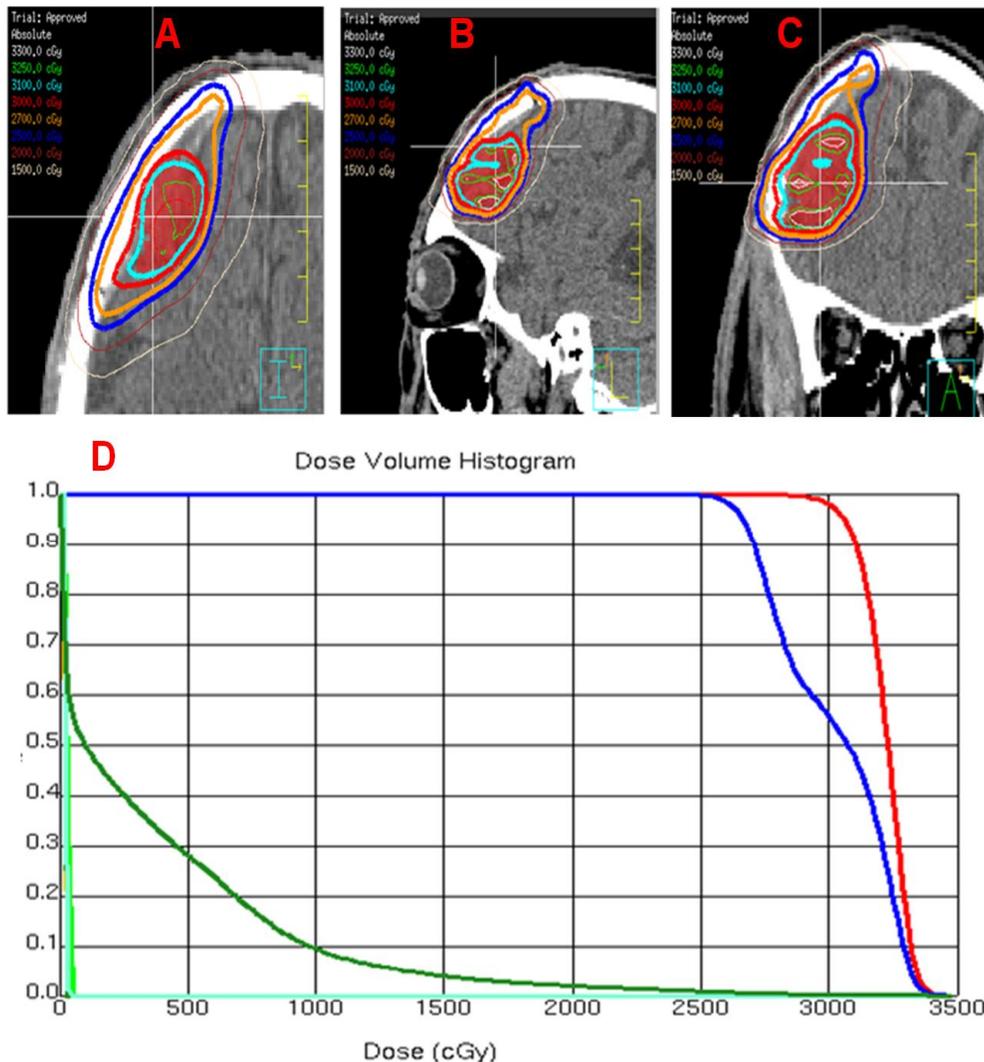


Fig. 1. Simultaneous integrated boost hypofractionated stereotactic radiosurgery of 30 Gy (red line) to primary tumor resection cavity and dura in close contact and 25 Gy (dark-blue line) covering surgical tract and dura in 5 fractions: A) Axial view, B) Sagittal view, C) Coronal view, and D) Plan dose-volume histogram

Table 1. Prescription recommendations per literature

Resection cavity maximum size or volume ^{15,19,33}	Number of fractions			Clinical target volume (CTV) ^{48,60} Fusion with postoperative (± preoperative) T1-weighted gadolinium-enhanced axial magnetic resonance imaging scans recommended			
	1 ^{15,19,33}	3 ^{40,55}	5 ^{40,50,54}	Cavity	Surgical tract	Preoperative dura contact	Preoperative venous sinus contact
≤2.6 cm ≤ 10 cc	16-18 Gy	24-30 Gy	25-35 Gy	Entire contrast-enhancing surgical cavity	Entire surgical tract	Plus 5-10 mm margin along the bone flap beyond the initial contact	Plus 1-5 mm margin along the sinus
2.7 - 3 cm 10.1-15 cc	14-17 Gy						
3 - 3.3 cm 14.4–19.9 cc	12-15 Gy					Plus 1-5 mm margin along the bone flap	
3.3 - 3.8 cm 20.0–29.9 cc	12-14 Gy						
≥ 3.9 cm	12 Gy						
≥30.0 cc							

Table 2. Ongoing and completed trials for postoperative stereotactic radiosurgery

Status	Title	Design	Phase	Center	Planned accrual	ClinicalTrials.gov Identifier
Ongoing	Stereotactic radiotherapy of the resection cavity of brain metastases vs. post-operative whole-brain radiotherapy (ESTRON)	PO-SRS vs. WBRT	2	University of Heidelberg		NCT03285932
Ongoing	Pre-operative SRS or post-operative SRS in treating cancer patients with brain metastases	QOL Assessment Questionnaire SRS	3	MD Anderson Cancer Center	86	NCT03741673
Ongoing	Neo-adjuvant vs. post-operative stereotactic radiosurgery for operable metastatic brain tumors	Conventional Surgery QOL Assessment Questionnaire SRS	3	Mayo Clinic	140	NCT03750227
Ongoing	Stereotactic radiation and nivolumab in the management of metastatic breast cancer brain metastases	Nivolumab + PO-SRS	1	H. Lee Moffitt Cancer Center and Research Institute	12	NCT03807765
Ongoing	Stereotactic radiosurgery compared to observation in treating patients with brain metastases	SRS	3	MD Anderson Cancer Center	132	NCT00950001

Status	Title	Design	Phase	Center	Planned accrual	ClinicalTrials.gov Identifier
Completed	A trial of postoperative whole-brain radiation therapy vs. salvage stereotactic radiosurgery therapy for metastasis	WBRT vs. salvage SRS	3	Multicenter, Japan	270	NCT00280475
Completed	Phase II trial of stereotactic radiosurgery boost following surgical resection for brain metastases	SRS	2	Memorial Sloan-Kettering Cancer Center	51	NCT00587964
Completed	Bendamustine and radiation therapy in treating patients with brain metastases caused by solid tumors	Bendamustine Surgery	1	Ohio State University Medical Center	18	NCT00837928
Completed	Surgery versus radiosurgery to treat metastatic brain tumors	SRS vs. surgery	4	National Institute of Neurological Disorders and Stroke (NINDS)	130	NCT00075166
Completed	Radiation therapy following surgery to remove brain metastases	Surgery PO-SRS	Pilot	UCLA Jonsson Comprehensive Cancer Center	20	NCT00003320

Abbreviations: PO-SRS: Postoperative stereotactic radiosurgery, WBRT: Whole-brain radiotherapy, QOL: Quality of life

Table 3. Results of randomized trials of postoperative stereotactic radiosurgery

Trial	Arms	Patients (N)	Dose	OS	LC	EIBF	Comments
Brennan et al [30]	Sx + POSRS	39 with 50 BM, 40 treated with POSRS	1 × 18 Gy	NS	POSRS had a significantly lower incidence of LF (P=.008) Tumors ≥ 3 cm with superficial dural/pial involvement demonstrate the highest risk of LF.	NA	POSRS is associated with high rates of local control, especially for deep BM < 3 cm.
	Sx		-	NS		NA	
Kepka et al. [31]	Sx + POSRS	29	1 × 15 Gy or 5 × 5 Gy	2-year neurological death rates, 66% vs. 31%, for POSRS and WBRT arms, respectively, P = 0.015.	NA	NA	Non-inferiority of POSRS was not demonstrated in this underpowered study
	Sx + WBRT	30	10 × 3 Gy		NA	NA	
Mahajan et al. [19]	Sx + POSRS	64	1 × 12-16 Gy	17 months	12 months LC: 72%	67%	POSRS in patients who have had complete resection of 1, 2,
	Sx	68	-	17 months	12 months LC: 45%	67%	

Trial	Arms	Patients (N)	Dose	OS	LC	EIBF	Comments
Brown et al. [33]	Sx + POSRS	98	1 × 12-20 Gy	11.5 months	Median surgical bed relapse-free survival: 7.5 months	Overall 12 months ICLF: 45.3%	or 3 BM notably lowers local recurrence compared with that Sx alone Decline in cognitive function was more frequent with WBRT than with POSRS with no difference in OS
	Sx + WBRT	96	10 × 3 Gy or 15 × 2.5 Gy	11.8 months	Median surgical bed relapse-free survival: 7.7 months	Overall 12 months ICLF: 11.4%	

Abbreviations: OS: Overall survival; LC: Local control; EIBF: Extra-cavity in brain failures; Sx: Surgery; POSRS: Postoperative stereotactic radiosurgery; BM: Brain metastases; NS: Not significant; NA: not applicable; LF: Local failure; WBRT: Whole-brain radiotherapy; ICLF: Intracranial local failure; Gy: Gray

dose of 16-18 Gy or by hypo fractionated PO-SRS to any size of cavities in 3 fraction to 24-27 Gy or 5 fractions to 25-30 Gy.

2.8 Follow up after Adjuvant SRS

Almost all PO-SRS literature of resected BMs showed a high risk of new BMs elsewhere in the brain and recommended the importance of close follow-up and surveillance [36,38,51]. Choi et al. declared a distant brain failure rate of 54% at 1 year [51]. Jagannathan et al. announced for their GK series that 72% of the treated patients required additional SRS for 140 new (metachronous) BMs at a median radiographic follow-up duration of 14 months [58]. Do et al, in their retrospective review, displayed that 63% of treated patients developed new BMs at distant brain sites [49]. Mahajan et al, in their prospective randomized trial, revealed that the 12-month time to distant brain recurrence was 33% in the observation group and 42% in the PO-SRS group which required intervention [19]. In the largest adjuvant SRS series, Shi et al documented 12-month overall distant intracranial and distant brain failure rates of 44% and 37%, respectively [40].

Enlightened with the above mentioned evidence, it is clearly evident that a close follow-up is undoubtedly indicated for PO-SRS patients to be able to properly manage the highly morbid and mortal elsewhere in brain failures. Therefore, NCCN guidelines recommends to obtain cranial MRI every 3 months for the first year and 4-6 months thereafter for such patients in the absence of neurological symptoms [59].

3. DISCUSSION AND CONCLUSIONS

There seems to be no magical decision tool for the ultimate treatment decision for patients presenting with BMs, and the management should always be discussed with the patient and his/her legal caretakers for a common ground focused on the risk-benefit ratio of the accessible treatment alternatives. The risk-benefit balance needs to be between the intracranial recurrence risk and the hazard for a significant deterioration in the neurocognitive functions. The recent implementation of the PO-SRS applications to the treatment algorithm of resected BMs has reputedly enhanced the local control at the surgical resection bed in comparison to observation or WBRT (Table 3). The omission of upfront WBRT did not threaten the overall survival outcomes, even though the risk for the

local and distant brain failures increased modestly. The omission of WBRT led to lessened cognitive deterioration and resultant more enjoyable quality of life measures. Therefore, PO-SRS for resected BMs should be perceived as a standard management with level I evidence, while the omission of WBRT mandates the close and dedicated contrast-enhanced and thin-slice volumetric MRI follow-ups for the early diagnosis of presumable tumor cavity and elsewhere in brain recurrences and for their timely salvage interventions.

Trials sound guiding us to fine-tune in target delineation and dose fractionation (single vs. hypofractionated PO-SRS) to optimize the local control, considering the risk of LMD based on the surgical tract and the sense of balance in treatment prescription based on the cavity size with hypofractionation to decrease the risk of RN despite higher biologically effective dose (such as 24–27 Gy in 3 fractions or 25-35 Gy in 5 fractions [60]. In conclusion, we recommend evidence-based optimization in the postoperative setting of resected BMs based on physical, mental, cognitive and neurological basal performance status, and location, volume, symptom and number burden of BMs, in the era of postoperative SRS being one of the care standard options with level I evidence. However, as depicted in Table 2, the ongoing trials on the utility of PO-SRS alone or in conjunction or concurrent with the other treatment modalities, such as the novel targeted agents or immune theapeutics will unquestionably enhance our knowledge for the selection of the best-fit treatment option(s) with the least toxicity but highest local and overall in brain control rates in an individual patient basis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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