Mini-Review | Palliative Medicine and Palliative Care for Incurable Cancer

Reirradiation of metastases of the central nervous system: part 1—brain metastasis

Dirk Rades[1], Charles B. Simone II[2], Henry C. Y. Wong[3], Edward Chow[4], Shing Fung Lee[5], Peter A. S. Johnstone[6]

[1]Department of Radiation Oncology, University of Lübeck, Lübeck, Germany; [2]New York Proton Center, New York, NY, USA; [3]Department of Oncology, Princess Margaret Hospital, Kowloon West Cluster, Hospital Authority, Hong Kong, China; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; [5]Department of Radiation Oncology, National University Cancer Institute, National University Hospital, Singapore, Singapore; [6]Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL, USA

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Correspondence to: Dirk Rades, MD, FASTRO. Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Email: dirk.rades@uksh.de.

Abstract: Because of improved survival of cancer patients, more patients irradiated for brain metastases develop intracerebral recurrences requiring subsequent courses of radiotherapy. Five studies focused on reirradiation with whole-brain radiation therapy (WBRT) after initial WBRT for brain metastases. Following the second WBRT course, improvement of clinical symptoms was found in 31–68% of patients. Rates of neurotoxicity, such as encephalopathy or cognitive decline, were reported in two studies (1.4% and 32%). In another study, severe or unexpected adverse events were not observed. Survival following the second WBRT course was generally poor, with median survival times of 2.9–4.1 months. The survival prognosis of patients receiving two courses of WBRT can be estimated by a scoring tool considering five prognostic factors. Three studies investigated reirradiation with single-fraction stereotactic radiosurgery (SF-SRS) following primary WBRT. One-year local control rates were 74–91%, and median survival times ranged between 7.8 and 14 months. Rates of radiation necrosis (RN) after reirradiation were 0–6%. Seven studies were considered that investigated re-treatment with SF-SRS or fractionated stereotactic radiation therapy (FSRT) following initial SF-SRS or FSRT. One-year local control rates were 60–88%, and the median survival times ranged between 8.3 and 25 months. During follow-up after reirradiation, rates of overall (asymptomatic or symptomatic) RN ranged between 12.5% and 30.4%. Symptomatic RN occurred in 4.3% to 23.9% of cases (patients or lesions). The risk of RN associated with symptoms and/or requiring surgery or corticosteroids appears lower after reirradiation with FSRT when compared to SF-SRS. Other potential risk factors of RN include the volume of overlap of normal tissue receiving 12 Gy at the first course and 18 Gy at the second course of SF-SRS, maximum doses ≥40 Gy of the first or the second SF-SRS courses, V12 Gy >9 cm^3 of the second course, initial treatment with SF-SRS, volume of normal brain receiving 5 Gy during reirradiation with FSRT, and systemic treatment. Cumulative EQD2 ≤100–120 Gy^2 to brain, <100 Gy^2 to brainstem, and <75 Gy^2 to chiasm and optic nerves may be considered safe. Since most studies were retrospective in nature, prospective trials are required to better define safety and efficacy of reirradiation for recurrent or progressive brain metastases.

Keywords: Brain metastasis; reirradiation; whole-brain radiotherapy; stereotactic radiosurgery (SRS); fractionated stereotactic radiation therapy (FSRT)

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Introduction

Many patients with brain metastases receive radiotherapy alone, either as whole-brain radiation therapy (WBRT) with or without a boost to metastatic sites or as highly-conformal radiotherapy such as single-fraction stereotactic radiosurgery (SF-SRS) or fractionated stereotactic radiation therapy (FSRT) (1,2). Due to prolongation of the survival of cancer patients by novel systemic therapies and due to new radiotherapy techniques allowing better sparing of the normal tissues, the number of patients receiving reirradiation of, e.g. brain metastases, has increased (3-5). Reirradiation of brain metastases may pose a challenge for radiation oncologists, because cumulative radiation doses of the first and second course may be above the tolerance doses of important structures including brain stem and optic pathways. In this narrative review, outcomes and toxicities of reirradiation for brain metastases are described. The article addresses several points, including the clinical effect of reirradiation of brain metastases on patients, side effects, survival time, presence of radiation necrosis (RN), and reirradiation after which type of primary radiotherapy. In order to contribute to these points, a comprehensive search on PubMed was performed from 1980 to 2023 using the terms "brain metastasis and re-irradiation", "brain metastases and re-irradiation", "brain metastasis and reirradiation", and "brain metastases and reirradiation".

Tolerance doses of the brain in general, brain stem, and optic pathways

According to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), maximum doses of conventionally-fractionated 3D conformal radiotherapy to the brain of <60, 72, and 90 Gy were associated with probabilities of symptomatic brain necrosis <3%, 5% and 10%, respectively (6). A maximum dose of 54 Gy and a dose <64 Gy to <1 cm^3 to the brainstem were associated with a <5% risk of necrosis or neuropathy, and maximum doses to the optic nerves or chiasm of <55, 55–60, and >60 Gy were associated with probabilities of optic neuropathy of <3%, 3–7% and >7–20%, respectively. For SF-SRS, V12 <5–10 cm^3 was associated with a risk of symptomatic brain necrosis <20%, a maximum dose to the brain stem (acoustic tumors) <12.5 Gy with a risk of necrosis or neuropathy <5%, and a maximum dose to the optic nerve or chiasm <12.5 Gy with a risk of optic neuropathy <10% (6).

Additional risk factors for RN include size and location of the metastatic lesion(s) and presence or absence of previous SF-SRS (7-10). Mohammadi *et al.* investigated 896 patients with brain metastases ≤2.0 cm (3,034 lesions) treated with one or more courses of SF-SRS, and found lesions >1.0 cm, location in the corpus callosum, and lesions from less common primary tumors (other than lung cancer, breast cancer, renal cell carcinoma, and melanoma) to be independent prognostic factors for radiographic RN (7). Moreover, size and location were independently associated with symptomatic RN (SRN). Ohtakara *et al.* identified "location grade" as an additional risk factor for brain necrosis (8). They defined three grades of location, namely depth ≤5 mm from brain surface (grade 1), depth >5 mm from brain surface (grade 2), and central (grade 3). Central locations included brainstem, cerebellar peduncle, diencephalon, and basal ganglion. Milano *et al.* summarized data of 51 reports on arteriovenous malformations and brain metastasis (9). For SF-SRS of brain metastasis, the volume (including target volumes) receiving 12 Gy was associated with SRN. Volumes of 5, 10, and >15 cm^3 were associated with necrosis rates of approximately 10%, 15%, and 20%, respectively. In another review of Milano *et al.* evaluating patients receiving primary irradiation with SF-SRS or FSRT, 10 Gy/1 F, 20 Gy/3 F, and 25 Gy/5 F (maximum point doses) were associated with a risk of radiation-induced optic neuropathy <1% (10).

Tolerance doses of reirradiation to the brain and potential risk factors for RN

Mayer and Sminia investigated SRN in patients reirradiated for glioma and found that SRN occurred after cumulative EQD2 >100 Gy^2 (11). Stiefel *et al.* reported the data of 76 patients reirradiated for primary brain tumors (n=34) or brain metastases (n=42) (12). They concluded that cumulative EQD2 ≤120 Gy^2 to the brain, <100 Gy^2 to the brainstem, and <75 Gy^2 to chiasm and optic nerves were both effective and safe.

Regarding risk factors for RN, Minniti *et al.* found that a volume of overlap ≥10 cm^3 of normal tissue receiving 12 Gy at the first and 18 Gy at the second course of SF-SRS was significantly associated with RN when compared to <10 cm^3 (53% *vs.* 15%, P=0.02) (13). In another study, an increased risk of SRN was significantly associated with maximum doses ≥40 Gy (*vs.* <40 Gy) of the first (22% *vs.* 5%, P<0.025) or the second (23% *vs.* 6%, P<0.025) SF-SRS course and V12 Gy >9 cm^3 (*vs.* ≤9 cm^3) of the second course

Table 1 Results of studies using WBRT for reirradiation of brain metastases following primary WBRT

Reference	No. of patients	Regimen of 1st WBRT course	Regimen of 2nd WBRT course	Rate of improvement of clinical symptoms	Median survival after re-RT
Sadikov (17) [2007]	72	20 Gy/5 F	Mainly 20–25 Gy/8–10 F, 20 Gy/10 F, or 15 Gy/5 F	31%	4.1 months
Akiba (18) [2012]	31	Median 30 Gy/10 F	Median 30 Gy/10 F	68%	4 months
Ozgen (19) [2013]	28	Median 30 Gy/10 F	Median 25 Gy/10 F	39%	3 months
Lai (20) [2018]	23[a]	Median 30 Gy/10 F	Median 30 Gy/10 F	56.5%	2.9 months
Logie (21) [2017]	205	Mainly 20 Gy/5 F	Mainly 20 Gy/5 F	Not reported	3.6 months

[a], breast cancer patients. WBRT, whole-brain radiotherapy; re-RT, reirradiation.

(21% *vs.* 4%, P<0.025) (14). In the univariable analysis of Yan *et al.*, initial SF-SRS (*vs.* FSRT) and targeted therapies or immunotherapy were identified as potential prognostic factors for SRN (15). However, both factors were not significant on multivariable analysis. In the multivariable analysis of Touati *et al.*, the volume of normal brain tissue receiving 5 Gy during reirradiation with FSRT, the dose of the first course of stereotactic radiotherapy, and concurrent systemic treatment were independent risk factors of RN (16).

Reirradiation with WBRT following WBRT

Five studies were included that focused on reirradiation with a second course of WBRT following primary WBRT for brain metastases. In the retrospective study by Sadikov *et al.*, 72 patients received WBRT mainly with 25 Gy/10 F (n=22), 20 Gy/10 F (n=12), 15 Gy/5 F (n=11), or 20 Gy/8 F (n=10) following primary WBRT with 20 Gy/5 F (17). Twenty-two of 55 evaluable patients (40%) showed at least partial clinical improvement to reirradiation, and another 15 patients (27%) remained stable. Late toxicity was not well documented. Akiba *et al.* presented 31 patients receiving two courses of WBRT, each with median 30 Gy/10 F (18). Symptoms improved in 21 patients (68%). Following reirradiation, brain atrophy was observed in 23 patients (74%) on magnetic resonance imaging. Ten patients (32%) developed grade ≥2 encephalopathy or cognitive decline during the median follow-up interval of 3 [interquartile range (IQR), 1–13] months. In the study by Ozgen *et al.*, first and second courses of WBRT for multiple brain metastases (median 9.5 months, IQR, 3–27 months) were delivered to a median of 30 Gy/10 F and median 25 Gy/10 F, respectively (19). Relief of symptoms occurred in 39% of patients. Severe or unexpected adverse events were not observed. Lai *et al.* presented the data of 23 breast cancer patients receiving whole-brain reirradiation to a median dose of 20 Gy/10 F after median 12.6 (IQR, 10.2–15.0) months following primary WBRT to a median of 30 Gy/10 F (20). Improvement of clinical symptoms was observed in 13 patients (56.5%) at 1 month following the second WBRT course. The median survival times following reirradiation in these four studies and the study of Logie *et al.* were poor and ranged between 2.9 and 4.1 months (17-21). Results of studies investigating reirradiation with WBRT following primary WBRT are shown in *Table 1*.

The survival prognosis of patients with brain metastases receiving a second course of WBRT was reported to be associated with Karnofsky performance score (KPS), primary tumor type, interval between the first and second course of WBRT, controlled primary tumor, and extra-cranial metastasis (18,19,21). A higher KPS was associated with better survival in all three studies (18,19,21). In one study, patients with non-small cell lung cancer (NSCLC) had better survival prognoses than breast cancer patients on multivariate analysis (19). In the multivariate analysis of another study, patients with small-cell lung cancer (SCLC) had worse outcomes than patients with NSCLC, breast cancer, or other tumors (21). In two studies, longer interval between both WBRT courses of (≥9.5 and ≥9 months, respectively) was a predictor of improved survival (19,21). Moreover, in one study, control of the primary tumor, and absence of extra-cranial metastasis were independently associated with improved survival (21). To estimate the survival prognoses of reirradiated patients, a scoring system was developed by Logie *et al.*, considering five unfavorable prognostic factors, including KPS <80, SCLC, an interval between both WBRT courses <9 months, uncontrolled primary tumor, and extra-cranial metastasis (21). One point was given for each unfavorable factor, and three prognostic groups were designed, namely 1–2, 3, and 4–5 points.

Table 2 Results of studies using SF-SRS for reirradiation of brain metastases following primary WBRT

Reference	Patients No. [lesions]	Regimen of primary WBRT	Regimen of SF-SRS for re-RT	Local control rate after re-RT (SF-SRS)	Median survival after re-RT (SF-SRS)	Complications after re-RT (SF-SRS)
Noël (22) [2001]	54 [97]	Mainly 30 Gy/10 F	Median 16.2 Gy/1 F	91% (at 1 year)	7.8 months	No major complications
Maranzano (23) [2012]	69 [150]	Not reported	Median 20 Gy/1 F	74% (at 1 year)	10 months	6% asymptomatic radiation necrosis
Maranzano (25) [2019]	59 [109]	20 Gy/5 F or 30 Gy/10 F	Median 18 Gy/1 F	81% (at 2 years)	14 months	No radiation necrosis after 1st re-RT

SF-SRS, single-fraction stereotactic radiosurgery; WBRT, whole-brain radiotherapy; re-RT, reirradiation.

Corresponding median survival times were 7.2, 3.0, and 2.2 months (P<0.001).

Reirradiation with SF-SRS following WBRT

Three studies have investigated reirradiation with SF-SRS following primary WBRT. Noël *et al.* reported the results of 54 retrospectively evaluated patients (97 lesions) who received SF-SRS to a median of 16.2 Gy (median minimal dose to gross disease) following WBRT that was most commonly delivered to 30 Gy/10 F (65% of patients) or doses ≥40 Gy using 1.8–2.0 Gy per fraction (20% of patients) (22). The 1-year local control rate after reirradiation was 91%, and the median survival time was 7.8 months. Adverse events were minimal, with two patients reporting headaches and two patients developing grade 2 alopecia. Major complications were not observed during the follow-up of median 9 (IQR, 1–57) months. In 2012, Maranzano *et al.* presented a retrospective study of 69 patients (150 lesions) treated with SF-SRS (median 20 Gy) following primary WBRT (23). For lesions of ≤20, 21–30, and 30–40 mm, doses of SF-SRS were most commonly 24, 18, and 15 Gy, as suggested by the RTOG protocol 90-05 (24). Of the 52 patients with favorable neurologic functional scores (NFS; 0–1), 1 patient (2%) improved and 46 patients (88%) maintained their scores. Of 17 patients with unfavorable NFS (2–3), only three patients (18%) improved. The 1-year local control rate after SF-SRS was 74%, and median survival time was 10 (IQR, 1–82) months. Four patients (6%) developed asymptomatic RN [suspected on magnetic resonance imaging (MRI), confirmed by Single photon emission computed tomography/computed tomography (SPECT-CT)] 5, 5, 8, and 14 months after reirradiation. In addition, Maranzano *et al.* performed a prospective phase 2 trial of 59 patients (109 lesions) with favorable prognostic factors including KPS ≥70, NFS 0–1, and maximum diameter of lesions ≤20 mm (25). Reirradiation was performed using SF-SRS to a median dose of 18 (IQR, 10–20) Gy and median 15 (IQR, 6–169) months after primary WBRT with 30 Gy/10 F (73% of patients) or 20 Gy/5 F (27%). Twenty-five patients (42%) responded to reirradiation, whereas the other 34 patients (58%) had stable disease. One-year and 2-year local control rates after SF-SRS were both 81%, and the median survival time was 14 (IQR, 1–107) months. RN was not observed after the first reirradiation with SRS during the follow-up period of 14 (IQR, 1–107) months. Results of studies investigating reirradiation with SF-SRS following primary WBRT are summarized in *Table 2*.

Reirradiation with SF-SRS or FSRT following primary SRS or FSRT

Seven studies were considered that investigated reirradiation with SF-SRS or FSRT following primary SRS or FSRT. In the study by Minniti *et al.* of 43 patients (47 lesions), reirradiation for recurrent or progressive brain metastases was performed with FSRT (24 Gy/3 F for lesions <20 mm, 21 Gy/3 F for lesions ≥20 mm) median 17 (IQR, 6–56) months following SF-SRS (13). One-year and 2-year local control rates after reirradiation were 70% and 60%, and survival rates were 37% and 20%. The median survival time was 10 months. For nine lesions (19%), radiologic changes suggestive of RN were found after a median of 8 (IQR, 5–15) months. Six patients (14%) experienced neurologic deficits of grade 2 or 3 due to RN requiring surgery or high-dose dexamethasone. McKay *et al.* administered a second course of SF-SRS to a median dose of 20 (IQR, 14–22) Gy to the same lesions following SF-SRS to a median of 20 (IQR, 12–24) Gy in 32 patients (46 lesions) (26). One-year local control and survival rates after reirradiation were 79% and 70%, respectively. Median follow-up after the second course

of SF-SRS was 24 (IQR, 2–124) months. During this period, overall RN and SRN occurred in 14 (30.4%) and 11 (23.9%) lesions, respectively. RN was always diagnosed by imaging and additionally confirmed by biopsy in 3 patients (9%). The study of Koffer *et al.* included 22 patients (24 lesions) treated with a second course of SF-SRS for locally recurrent brain metastases (27). Median doses were 18 Gy for the first course and 15.5 Gy for the second course. Six-month and 12-month local control rates after the second course of SF-SRS were 94.1% and 61.1%, respectively. The median survival time was 8.8 months. RN was identified in 4 of 24 lesions (16.7%) by MR spectroscopy (1 lesion) or biopsy (3 lesions). SRN was not mentioned. Holub *et al.* evaluated 47 patients (55 lesions) re-treated with SF-SRS or FSRT for locally recurrent brain metastases after SF-SRS or FSRT (28). The median interval between both treatments was 11.2 (IQR, 7.9–20.5) months. For the first course, 74.5% of patients received FSRT to 18–35 Gy/3–5 F, and 25.5% received SF-SRS to 18–20 Gy. Reirradiation was delivered to 18–20 Gy using SF-SRS in 21.3% of patients or FSRT (15–35 Gy/2–5 F) in 78.7% of patients. Eight patients (17%) received WBRT prior to the first (n=6) or second (n=2) radiotherapy course. Surgery was performed for 22 lesions (40%) prior to the first course (n=10), the second course (n=11), or both (n=1). Six-month and 1-year local control rates after reirradiation were 95% and 80%, respectively, and the median survival time was 9.2 months. RN was identified by MRI in 11 patients (23.4%), being symptomatic and treated with surgical resection in two patients (4.3%). Kowalchuk *et al.* evaluated a retrospective series of 102 patients (123 lesions) from eight centers receiving SF-SRS to a median dose of 18 (IQR, 16–18) Gy for local or marginal intracerebral recurrences following SF-SRS to a median of 19 (IQR, 18–20) Gy (14). Median periods of radiographic and clinical follow-up after the second course were 12 (IQR, 5.6–30.5) and 14 (IQR, 7–35) months, respectively. One-year and 2-year local control rates after reirradiation were 79% and 72%. Rates of overall RN (diagnosed by MRI), asymptomatic RN, and SRN were 20.3% (after median 5.4 months), 13.0% (after median 5.2 months), and 7.3% (after median 5.9 months). In 2023, Yan *et al.* presented the results of 91 patients (120 lesions), who received FSRT with 20–35 Gy/3–5 F for local recurrence after SF-SRS with 16–20 Gy or FSRT with 24–35 Gy/3–5 F (15). After re-treatment, 6-month and 12-month local control rates were 81.1% and 72.3%, and the median survival time was 15.9 months. During the follow-up period of median 13.4 (IQR, 1.1–111.1) months, radiographic RN was found for 19.2% of lesions, which was symptomatic in 7.5% (9 of 120 lesions). Touati *et al.* presented 32 patients (34 lesions) re-treated to 21–27 Gy/3 F or 30 Gy/5 F after local failure following SF-SRS or FSRT (16). One-year local control was 60%, and median survival 25 months. During follow-up of median 12 (IQR, 1–37) months, four patients (12.5%) developed RN, identified by multiparametric MRI and positron emission tomography (PET) imaging, after a median of 6 (IQR, 4–10) months, which was symptomatic in two patients (6.3%). Results of studies using SF-SRS or FSRT following primary SF-SRS or FSRT are given in *Table 3*.

Conclusions

A considerable number of patients irradiated for brain metastases develop intracerebral recurrences and require reirradiation. A second course of WBRT led to an improvement of clinical symptoms in 31–68% of patients. Survival following the second WBRT course was generally poor. Individual prognoses can be estimated with a specific survival score. Reirradiation with SF-SRS after WBRT resulted in 1-year local control and RN rates of 74–91% and 0–6%, respectively. One-year local control rates after SF-SRS or FSRT following initial SF-SRS or FSRT were 60–88%. RN occurred in 12.5–30.4% and SRN in 4.3–23.9% of cases (patients or lesions). The risk of RN associated with symptoms and/or requiring surgery or corticosteroids appears lower after reirradiation with FSRT (*vs.* SF-SRS). Other potential risk factors of RN were identified, including dose-volume parameters and systemic treatment. In general, cumulative EQD2 ≤100–120 Gy^2 to brain, <100 Gy^2 to brainstem, and <75 Gy^2 to chiasm and optic nerves may be considered safe. During the interpretation of this mini-review, its limitations that are typical for narrative reviews should be considered. Narrative reviews may not be reproducible due to the risk of selection biases related to the preferences and perspectives of the authors, particularly regarding the way of screening, sampling, and analyzing the data from literature (29). Moreover, narrative reviews are selective and often do not include a comprehensive search of all available evidence (29). This mini-review bears an additional risk of selection biases due to the retrospective nature of many studies included. Acknowledging the limitations of this review, reirradiation of brain metastases appears effective and also safe, provided the constraints of the organs at risk are considered. A second course of WBRT may be used in patients with poor estimated survival, poor

Table 3 Results of studies using SRS or FSRT for reirradiation of brain metastases following primary SRS or FSRT

Reference	Patients No. [lesions]	Regimen of 1st SRS/FSRT course	Regimen of 2nd SRS/FSRT course	Local control at 1 year after re-RT	Median survival after re-RT	Rates of RN and SRN after re-RT
Minniti (13) [2016]	43 [47]	single-fraction SRS	21–24 Gy/3 F	70%	10 months	RN in 19% of lesions SRN in 14% of patients (neurologic deficits grade ≥2)
McKay (26) [2017]	32 [48]	Median 20 Gy/1 F	Median 20 Gy/1 F	79%	70% (at 1 year)	RN in 30.4% of lesions SRN in 23.9% of lesions
Koffer (27) [2017]	22 [24]	Median 18 Gy/1 F	Median 15.5 Gy/1 F	61.1%	8.8 months	9.2% RN at 1 year SRN not reported
Holub (28) [2021]	47 [55]	Mainly FSRT (74.5%)	Mainly FSRT (79%)	80%	9.2 months	RN in 23.4% of patients and 21.8% of lesions SRN in 4.3% and 3.9%
Kowalchuk (14) [2022]	102 [123]	Median 19 Gy/1 F	Median 18 Gy/1 F	79%	Not reported	RN in 20.3% of lesions SRN in 7.3% of lesions
Yan (15) [2023]	91 [120]	16-28 Gy/1 F or FSRT	20-35 Gy/5 F	72.3%	15.9 months	RN in 19.2% of lesions SRN in 7.5% of lesions
Touati (16) [2023]	32 [34]	Not reported	21-27 Gy/3 F or 30 Gy/5 F	60%	25 months	RN in 12.5% of patients SRN in 6.3% of patients

SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiation therapy; re-RT, reirradiation; RN, overall radiation necrosis (asymptomatic + symptomatic); SRN, symptomatic radiation necrosis.

KPS, and/or a considerable number of lesions, mainly to alleviate symptoms. For patients with more favorable survival prognoses and/or a limited number of lesions, reirradiation with SRS or FSRT (following primary treatment with WBRT or SRS/FSRT) appears to be a better option, since it is associated with less neurocognitive decline than WBRT and can lead to significant longer-term control of the brain metastases. For these patients, reirradiation with FSRT may be preferable, since it appears to be associated with less SRN than SF-SRS. However, long-term toxicity monitoring and additional prospective trials are required to better define safety and efficacy of reirradiation for brain metastases.

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