TOPIC REVIEW

Single- and hypofractionated stereotactic radiosurgery for large (> 2 cm) brain metastases: a systematic review

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Abstract

Purpose Since frameless stereotactic radiosurgery (SRS) techniques have been recently introduced, hypofractionated SRS (HF-SRS) for large brain metastases (BMs) is gradually increasing. To verify the efficacy and safety of HF-SRS for large BMs, we aimed to perform a systematic review and compared them with SF-SRS.

Methods We systematically searched the studies regarding SF-SRS or HF-SRS for large (> 2 cm) BM from databases including PubMed, Embase, and the Cochrane Library on July 31, 2018. Biologically effective dose with the α/β ratio of 10 (BED_{10}), 1-year local control (LC), and radiation necrosis (RN) were compared between the two groups, with the studies being weighted by the sample size.

Results The 15 studies with 1049 BMs that described 1-year LC and RN were included. HF-SRS tended to be performed in larger tumors; however, higher mean BED_{10} (50.1 Gy_{10} versus 40.4 Gy_{10}, $p < 0.0001$) was delivered in the HF-SRS group, which led to significantly improved 1-year LC (81.6 versus 69.0%, $p < 0.0001$) and 1-year overall survival (55.1 versus 47.2%, $p < 0.0001$) in the HF-SRS group compared to the SF-SRS group. In contrast, the incidence of radiation toxicity was significantly decreased in the HF-SRS group compared to the SF-SRS group (8.0 versus 15.6%, $p < 0.0001$).

Conclusion HF-SRS results in better LC of large BMs while simultaneously reducing RN compared to SF-SRS. Thus, HF-SRS should be considered a priority for SF-SRS in patients with large BMs who are not suitable to undergo surgical resection.

Keywords Fractionation · Large brain metastasis · Stereotactic radiosurgery · Tumor control · Radiation toxicity

Introduction

Stereotacic radiosurgery (SRS) in brain metastases (BMs) has been performed for decades and is usually confined to small tumors. Large BMs have been hindered from SRS and treated with either surgical resection or conventional radiation therapy; however, recent advancements in frameless and image-guided SRS techniques have allowed fractionated SRS, and SRS for large BMs using fractionation has been increasingly performed for the last ten years [1].

The local control (LC) of single fraction SRS (SF-SRS) for BM has been well known to be linked to the prescription dose. Several authors reported that LC was significantly improved when the BMs were irradiated using SF-SRS with a minimal dose over 18 Gy [2, 3]. Additionally, a dose of ≥ 16 Gy is reportedly sufficient to achieve an acceptable LC, whereas a study that investigated the correlation between the prescription dose and the LC in BMs < 26 mm in a diameter (< 10 cm³ in a volume) recommended giving a dose ≥ 25 Gy to achieve a satisfactory LC [4]. The higher the radiation dose delivered to the BM, the better the LC attained, and overall, the 1-year LC of BMs after SF-SRS has been reported to roughly range from 80 to 90%: > 90% for small and non-small cell lung cancer with a median overall survival (OS) of 14 to 18 months [5, 6]; 86–94% for

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breast cancer with a median OS of 14.5 months [7]; 75–94% for melanoma [8]; and 94% for renal cell cancer [9]. Matsuo et al. reported that the minimal dose to the BMs (Dose$_{min}$) is the single most significant predictor of LC, and they recommended 25 Gy for BMs < 10 cm^3 and 20 Gy for BMs ≥ 10 cm^3 [4]. Shiau et al. also verified, from their study of the correlation between the prescription dose and LC, that the higher the dose delivered, the better the LC achieved [2]. Similarly, we are able to attain improved LC by radiation dose escalation; however, tumor size limits radiation dose escalation because the larger the tumor treated with SF-SRS is, the more likely local toxicity occurs, such as radiation-induced edema and radiation necrosis (RN). Therefore, to reduce the risk of RN to less than 3%, large tumors have generally been treated with a reduced radiation dose than the originally required dose, which frequently leads to local failure [2, 10–13]. According to a study of the relationship between the tumor volume, dose and local control performed by Richard et al., the stepwise reduction in marginal dose to tumor according to increasing tumor size, from 21–25 Gy, 18–20 Gy, to 12–15 Gy, caused a remarkable decline of 1-year LC from 82, 64, to 37%, respectively [13]; however, since the introduction of fractionated SRS, SRS practice has been shifting towards maintaining an adequate marginal dose through fractionation rather than dose reduction for large BMs, and favorable LC and toxicity have been reported by several institutes. Here, we aimed to perform a systematic review of SRS for large BMs over 2 cm in diameter (or 3 cm^3 in volume) to compare the efficacy and safety of the two treatment modalities of SF-SRS and hypofractionated SRS (HF-SRS).

Methods

Search strategy

We systematically searched the studies regarding SF-SRS or HF-SRS for large (> 2 cm) BM from databases including PubMed, Embase, and the Cochrane Library on July 31, 2018. The detailed search strategy is presented in Supplementary Table 1. A manual search of reference lists from previous relevant studies and reviews was also conducted to further identify relevant literature.

Eligibility criteria

Both retrospective and prospective studies performed in humans were included in this analysis, with case reports, conference abstracts, and review articles being excluded. Studies written in a language other than English were excluded. If the contents of the abstract were considered compatible with this study, the full text of the study was

entirely reviewed by two independent researchers (EJL and ESP). This review was focused on large metastatic brain tumors ≥ 2 cm in diameter (or 3 cm^3 in volume) treated with either SF-SRS or HF-SRS. Hypofraction was defined as the number of fractions between 2 and 5. We considered radiation therapy as SRS if it was performed in a stereotactic manner with a safety margin within 3 mm even though it was described as "stereotactic radiotherapy". The primary end point was 1-year LC after radiosurgery, and the secondary end point was RN. Only studies that reached a consensus between the two authors were included in the systematic review.

Data extraction

Two reviewers (EJL and ESP) independently reviewed the full text of each included study and extracted data using a standardized form. The abstracted data included the name of the author, publication year, sample size, tumor size (mean and range), study design, treatment modality, SRS dosimetry, 1-year LC, 1-year number at risk, 1-year OS, RN, and medical follow-up period. The biologically effective dose (BED) was estimated from the dose prescribed to the isocenter of the tumor using a linear-quadratic model assuming α/β to be 10 Gy [14].

Statistical analysis

After database searching and data extraction, we performed a systematic review in which the studies reported treatment results after SF-SRS or HF-SRS for large (> 2 cm) BMs. Selected study populations were divided into 2 categories by treatment modality, SF-SRS and HF-SRS. To compare the integrated data of the SF-SRS and HF-SRS groups, Mann–Whitney U tests [15] were performed for continuous nonparametric variables, with the studies being weighted by the sample size. Differences with p values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS v.22.0 (SPSS Inc., Chicago, IL).

Results

We found 289 articles from a search of PubMed, 240 from EMBASE, 22 from the Cochrane Library, and 1 additional article from manual searching. A total of 362 studies were identified after removing duplicates, and 347 potentially relevant articles were retrieved for full-text review. The 15 studies selected that described 1-year LC and RN for patients treated with SF-SRS or HF-SRS for BM ≥ 2 cm (or 3 cm^3), and data on 1049 BMs were extracted (Fig. 1) [16–30]. Among these 15 publications, five studies covered only BMs treated with SF-SRS [26–30], seven studies dealt

Fig. 1 The flow diagram of the literature search and study selection
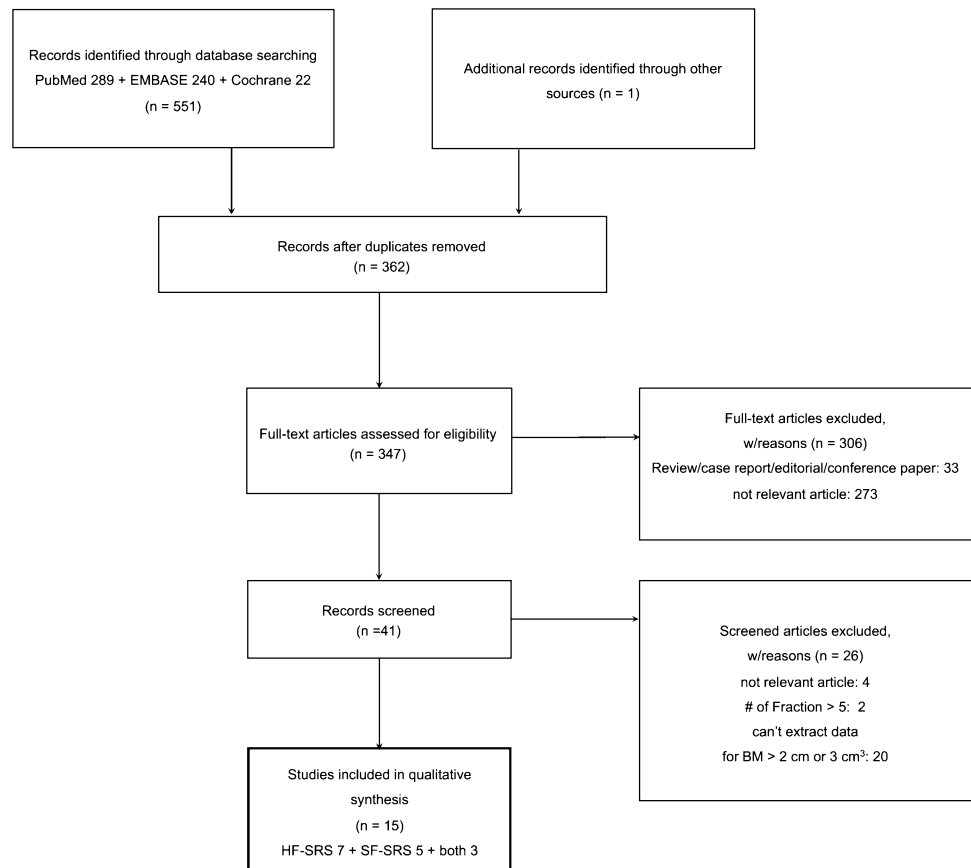
with only BMs treated with HF-SRS [16, 17, 19–21, 23, 24], and three studies included both BMs treated either SF-SRS or HF-SRS [18, 22, 25]. For the three studies that included both BMs treated with either SF- or HF-SRS, we collected data separately for SF- and HF-SRS groups.

The studies that were finally included in this review are summarized in Tables 1, 2. All studies had mixed primary cancer pathologies, with lung cancer being the majority, except the study conducted by Flannery and colleagues that included only BM from prostate carcinoma [27]. In the SF-SRS group, eight studies were included, encompassing 463 composite BMs, and ten studies with a composite BM number of 586 in the HF-SRS group. HF-SRS was mostly delivered daily on consecutive days. Three studies directly compared the outcomes of SF-SRS and HF-SRS in large BMs [18, 22, 25]. Minniti et al. performed SF-SRS and HF-SRS as primary treatments for 179 and 164 BMs > 2.0 cm in diameter, respectively [22]. The tumor size of the HF-SRS group ranged from 4.1 to 47.9 cm^3, which was significantly larger than that of the SF-SRS group (range, 3.1–24.1 cm^3; $p = 0.005$). In the SF-SRS group, 18 Gy (BED$_{10}$ = 50.4 Gy$_{10}$) was delivered for BMs of 2–3 cm and 15–16 Gy (BED$_{10}$ = 37.5–41.6 Gy$_{10}$) for BMs ≥ 3 cm, whereas in the HF-SRS group, 27 Gy was delivered in 3 fractions (BED$_{10}$ = 51.3 Gy$_{10}$) at 80–90% isodose line.

During a median radiologic follow-up of 10 months, BMs treated with SF-SRS recurred much more frequently than those treated with HF-SRS (16.6 vs 8%, $p = 0.03$), and the 1-year LC rate of SF-SRS was also significantly lower than that of HF-SRS (77 vs 91%, $p = 0.01$). On the other hand, RN occurred significantly more often in the SF-SRS group than in the HF-SRS group (20 vs 8%, $p = 0.008$). Propensity score matching analysis also demonstrated favorable outcomes in the HF-SRS group in terms of both LC ($p = 0.01$) and RN risk ($p = 0.005$). Feuvret et al. also reported the treatment results of SF-SRS and HF-SRS in BM > 3 cm in diameter [18]. In the SF-SRS group, 14 Gy (BED$_{10}$ = 33.6 Gy$_{10}$) was prescribed in 24 BMs with a GTV ranging from 4.5 to 33.1 cm^3, whereas in the HF-SRS group, 7.7 Gy per day was delivered for 3 consecutive days (BED$_{10}$ = 40.9 Gy$_{10}$) in 12 BMs with a GTV ranging from 12.5 to 52.5 cm^3. The size of tumors treated with HF-SRS was significantly larger than those treated with SF-SRS ($p = 0.02$). The 1-year LC rate tended to be superior in the HF-SRS group than in the SF-SRS group (100 vs 58%, $p = 0.06$). No RN was recorded in either SRS group during the 7-month median follow-up period. In contrast, another study that directly compared the SF- and HF-SRS for large BMs did not show a difference in either the 1-year LC (67 vs 75%, $p = 0.27$) or 1-year free from RN (85 vs 75%, $p = 0.25$) rates

Table 1 Summary of HF-SRS studies on large (> 2 cm) brain metastases

Author (year)	# of BMs	Tumor size	HF-SRS schedule	Mean BED_{10} (Gy_{10})	Margin (mm)	1-year LC (%)	1-year OS (%)	Radiation toxicity (%)	Median FU (mo)	Equipment
Aoyama (2003), [14]	68	> 3 cm³, ≤48.3 cm³	8.75 Gy×4 (over 4–6 days)	65.6	2	59	NA	NA	6	LINAC
Ogura (2012), [15]	14	3.67–15.38 cm³ (7.87±3.25)	7–8 Gy×5	60.4	1	91.7	43.6	7.1	8.5	Novalis
Wiggenraad (2012), [23]	65	<13 cm³, (n=18); 13–20 cm³, (n=16); >20 cm³, (n=31)	8 Gy×3 (in 8 days)	43.2	2	75	NA	NA	5.3	Novalis
Feuvret (2014), [16]	12	3.2–5.95 cm; 12.50–52.52 cm³	7.7 Gy×3 (daily)	40.9	2	100	58	0	7	LINAC
Murai (2014), [17]	61	2.5–4 cm/>4 cm	18–22; 22–27; 27–30 Gy in 3 Fx (daily)/21–25; 25–31; 31–35 Gy in 5 Fx (daily)	~47.9[b]	2	69	31	0	6	CyberKnife
Nagai (2014), [18]	24	3–18 cm³	7–7.2 Gy×4 (daily)	~48.6[a]	2	92	37	0	18	Helical tomotherapy
Kim (2016), [19]	40	>10 cm³ (Posterior fossa), >14 cm³ (3 cm) ≤50.3 cm³	5–11 Gy×2–4 (daily)	45.0	0	NA	66.7	2.7	13.4	Gamma Knife
Minniti (2016), [20]	164	4.1–47.9 cm³	9 Gy×3	51.3	2	90	56	8	29	LINAC
Navarria (2016), [21]	102	2.1–3 cm/3.1–5 cm	9 Gy×3/8 Gy×4 (daily)	54.5	3	96	69	5.8	14	LINAC
Marcrom (2017), [22]	36	3–5.5 cm (39 cm³)	5 Gy×5/6 Gy×5 (over 7- to 14-days)	42.8	1–3	61	NA	11.1	5	LINAC

BED biologically effective dose, *BM* brain metastasis, *FU* follow-up, *HF-SRS* hypofractionated stereotactic radiosurgery, *LC* local control, *LINAC* linear accelerator, *OS* overall survival

[a] Mean BED_{10} was approximately estimated using the mean marginal dose of 7.1 Gy per fraction

[b] Mean BED_{10} was approximately estimated using the mean marginal dose for each dose escalation group

Table 2 Summary of SF-SRS studies on large (> 2 cm) brain metastases

Author (year)	# of BMs	Tumor size range	Marginal dose (Gy)	Mean BED$_{10}$ (Gy$_{10}$)	Margin (mm)	1-year LC (%)	1-year OS (%)	Radiation toxicity (%)	Median FU (mo)	Equipment
Kano (2009), [24]	10	3.1–18.0 cm³ (7.37±4.28)	11–18 (13.5±2.16)	32.2	0	All cases were censored	10	0	3	Gamma knife
Flannery (2010), [25]	10	6.3–17.2 cm³ (10.56±3.98)	12.5–18 (14.7±2.10)	36.3	0	62.5	28.6	NA	15	Gamma knife
Wiggenraad (2012), [23]	46	<13 cm³, n=11; 13–20 cm³, n=17; >20 cm³, n=18	15	37.5	2	67	NA	2.2	5.3	Novalis
Feuvret (2014), [16]	24	3.34–4.70 cm; 4.47–33.06 cm³	14	33.6	1	58	27	0	7	LINAC
Minniti (2016), [20]	179	3.1–24.1 cm³	18 for 2–3 cm; 15–16 for ≥3 cm	45.5	2	77	53	20	29	LINAC
Prabhu (2017), [26]	66	4.8–8.7 cm³	18 (16.5–18)	50.4	0–1	63.3	NA	12.3	10.3	LINAC
Cummings (2018), [27]	56	>20 mm, ≤30 mm	NA	NA	0	56	NA	NA	9.6	Novalis
	18	>30 mm, ≤27.7 cm³				38				
Wolf (2018), [28]	45	>20 mm, ≤30 mm	17 (12–20)	45.9	0	84	NA	NA	7.9	Gamma knife
	9	>30 mm, ≤21 cm³	16 (12–17)	41.6		67				

BED biologically effective dose, *BM* brain metastasis, *FU* follow-up, *LC* local control, *LINAC* linear accelerator, *OS* overall survival, *SF-SRS* single fraction stereotactic radiosurgery

[25]. For 46 BMs, 15 Gy was delivered in a single fraction ($BED_{10} = 37.5$ Gy_{10}), whereas 24 Gy was delivered in 3 fractions ($BED_{10} = 43.2$ Gy_{10}) for 65 BMs. The composite results of the SF-SRS and HF-SRS groups are compared in Table 3. The mean BED_{10} ($p = 0.021$) was significantly higher in the composite HF-SRS group, which led to significantly improved 1-year LC ($p = 0.031$) by 17% and 1-year OS ($p = 0.042$) by 22% compared with the composite SF-SRS group; however, the incidence of radiation toxicity was comparable between the two groups. When analyzed by applying a weight to each study's sample size, radiation toxicity occurred at a significantly lower rate in the HF-SRS group (8.0 versus 15.6%, $p < 0.0001$) with the higher mean BED_{10} (51.2 Gy_{10} versus 44.1 Gy_{10}, $p < 0.0001$), while and 1-year LC (81.6 versus 69.0%, $p < 0.0001$) and 1-year OS (55.1 versus 47.2%, $p < 0.0001$) were significantly higher (Table 4).

Discussion

The prolonged survival of cancer patients due to advancements of molecular biology and targeted therapies has inevitably led to a gradual increase in the incidence of brain metastasis including large-sized tumors [31, 32].

Such chemotherapy developments have raised the expectation that even patients with advanced disease status can be treated, which subsequently increases the requirement to treat BM actively compared to the past. Meanwhile, as patients inappropriate for surgical resection increase due to age, comorbidities, multiple lesions, and the need for continuity of chemotherapy, demand for SRS as an attractive alternative to surgery is increasing. Additionally, SRS has become the preferred treatment over WBRT for patients with a limited number of BMs because it is less likely to cause neurocognitive decline as a late adverse effect of radiation [33]; however, SRS, in which a single high-dose radiation is delivered to the target in the conventional approach, can cause radiation toxicity by irradiating a correspondingly large amount of surrounding normal tissues for the treatment of a large BM [34–36]. The development of radiation necrosis is correlated with the volume of normal brain tissue irradiated with a dose ≥ 12 Gy [37, 38]. Therefore, before the era of hypofractionated SRS, SRS was performed using a reduced radiation dose to avoid radiation toxicity; however, it may lead to treatment failure. Irradiation in fractionation is a basic strategy of conventional radiation therapy. Fractionation allows for tumor cells to be redistributed in the cell cycle and reoxygenated to make them radiosensitive, which enhances therapeutic efficacy and permits injured normal

Table 3 Comparison between the integrated results of SF-SRS and HF-SRS studies

Variables	SF-SRS (no. of study = 8)	HF-SRS (no. of study = 10)	p value (exact)
Composite sample size	463	586	
Tumor size	3.0–33.06 cm^3 (2–4.7 cm)	3–52.52 cm^3 (2–5.95 cm)	
Marginal dose	11–20 Gy	18–40 Gy in 2–5 fractions	
Mean BED_{10}	40.38 ± 6.52 Gy_{10} (32.15–50.40 Gy_{10})	50.07 ± 8.04 Gy_{10} (40.89–65.63y_{10})	0.021
1-Year local control	63.64 ± 13.06% (38–84%)	81.52 ± 15.67% (59–100%)	0.031
1-Year overall survival	29.65 ± 17.70% (10–53%)	51.61 ± 14.68% (31–69%)	0.042
Radiation toxicity	9.46 ± 9.07% (0–20%)	6.63 ± 7.97% (0–25%)	0.606
Median follow-up period (month)	10.89 ± 8.15 (3–29)	11.22 ± 7.66 (5.0–29)	0.965

BED biologically effective dos, *HF-SRS* hypofractionated stereotactic radiosurgery, *SF-SRS* single fraction stereotactic radiosurgery

Table 4 Comparison between the integrated results of SF-SRS and HF-SRS studies weighted by sample size

Variables	SF-SRS (# of study = 8)	HF-SRS (# of study = 10)	p value (Exact)
Composite sample size	463	586	
Tumor size	3.1–33.06 cm^3	3–52.52 cm^3	
Marginal dose	11 − 18 Gy	18–40 Gy in 2–5 fractions	
Mean BED_{10}	44.05 ± 5.05 Gy_{10} (32.15–50.40 Gy_{10})	51.23 ± 6.73 Gy_{10} (40.89–65.63 Gy_{10})	< 0.0001
1-Year local control	69.01 ± 10.93% (38–84%)	81.57 ± 13.77% (59–100%)	< 0.0001
1-Year overall survival	47.18 ± 12.21% (10–53%)	55.10 ± 13.02% (31–69%)	< 0.0001
Radiation toxicity	15.64 ± 6.21% (0–20%)	7.98 ± 7.22% (0–25%)	< 0.0001
Median follow-up period (month)	10.53 ± 7.23 (3–29)	14.77 ± 9.61 (5–29)	< 0.0001

BED biologically effective dos, *HF-SRS* hypofractionated stereotactic radiosurgery, *SF-SRS* single fraction stereotactic radiosurgery

tissues to be repaired and repopulated between treatments, decreasing radiation toxicity. Such a fractionation concept has also been applied to SRS in the form of HF-SRS in the hope of minimizing the risk of RN while maintaining BED to the tumors [33, 39]. Keeping a rigid frame on the head for several days was a considerable barrier to performing HF-SRS; however, since the frameless SRS system's advent more than a decade ago, HF-SRS has become a popular treatment for large BM. HF-SRS started with the hypothesis that it would lessen RN risk while achieving LC comparable to SF-SRS in treating large BM [18, 23, 32, 40, 41]. To verify these assumptions, we performed a systematic review of the efficacy and safety of HF-SRS compared to SF-SRS. Fifteen studies of large BM SRS were selected in total, including three studies directly comparing SF-SRS and HF-SRS. The composite data estimated that higher BED_{10} was delivered in the HF-SRS group, leading to a significant improvement in 1-year LC and 1-year OS, whereas decreasing the radiation toxicity rate, compared to the SF-SRS group. Also, planning target volume expansion with the 1–3 mm margin in HF-SRS may be associated with better LC in the HF-SRS group than the SF-SRS group that mainly did not include a margin. Lehrer et al. have recently performed a meta-analysis to compare the efficacy and safety between SF-SRS and HF-SRS for large BMs > 2 cm [32]. Fifteen studies with 1157 large BMs were included to analyze 1-year LC, including two studies that directly compared SF-SRS and MF-SRS. The authors stratified the analysis of 1-year LC by dichotomizing the tumor size between 2–3 cm diameter (4–14 cm^3) versus > 3 cm diameter (> 14 cm^3). Overall, meta-analyses did not confirm the superiority of HF-SRS in tumor control compared to SF-SRS; however, in the tumor size group of 2–3 cm diameter, there was a trend of better 1-year LC in the HF-SRS group than the SF-SRS group (92.9 versus 77.1%, $p = 0.18$). On the other hand, HF-SRS significantly reduced RN risk compared to SF-SRS in the tumor size group of 2–3 cm diameter, while there was a trend of reduced RN incidence in HF-SRS groups in the tumor size group of > 3 cm diameter. Since the present study included only three studies that directly compared the results between SF-SRS and HF-SRS, we were concerned that meta-analysis with limited data would provide unsatisfactory or biased results. Instead, we integrated the data from the SF-SRS and HF-SRS groups and compared the two groups via the Mann–Whitney U tests, which weighted the study sample size, resulting in a significant improvement in 1-year LC and decreased RN in the HF-SRS group over the SF-SRS group. Meanwhile, a recent prospective study comparing SF-SRS (n = 67, median dose 20 Gy) and HF-SRS (n = 38, median cumulative dose 35 Gy in 5 fractions) for 2.5–3 cm sized BMs reported a significant decrease in the incidence of RN (29.9 vs. 5.3%, $p < 0.001$) and improvement in 1-year LC (66.6 vs. 92.4%, $p = 0.028$) in the HF-SRS

groups with no difference in OS (median 13 months vs. 18 months, $p = 0.239$) between the two regimens [42].

Taken together, the results of SRS studies on large BMs indicate that HF-SRS may be a better treatment option for large BMs when considering efficacy and safety [43]. HF-SRS combines the advantages of SRS, which is precise administration of high-dose radiation to the target, and fractionation that allows repair, repopulation, redistribution, and reoxygenation [39, 44]. Whether it would be possible to lower the RN incidence even with a fraction number of 2–5 that is significantly smaller than that of conventional radiation therapy was unclear. Additionally, there was a concern that decreased dose per fraction in HF-SRS might lead to deteriorating tumor control in comparison with SF-SRS because high dose radiation in a single fraction is thought to be preferable to fractionated radiation therapy to control radioresistant tumors, such as BMs from hepatocellular carcinoma and melanoma. High-dose radiation is also believed to elicit severe damage in the tumor vessels, by which it exerts an additional antitumor effect [39]. Therefore, whether a decreased dose per fraction in HF-SRS would still preserve its influence on the vasculature was uncertain. However, a myriad of studies of HF-SRS has recently reported that fractionation with a limited number not only reduces RN risk even with administration of higher BED but also may improve tumor control despite decreased dose per fraction compared to SF-SRS. Radiation-induced DNA damage leads to accelerated senescence or cell death (apoptosis, autophagy, or necrosis) [45–47], depending on the radiation dose and radiosensitivity of the exposed tissue, with higher doses causing necrosis [48–50]. Unlike apoptosis, the necrosis process is associated with inflammation in surrounding normal tissue [51, 52]. The dose per fraction currently used in the HF-SRS seems to be high enough to treat malignant tumor cells but low enough not to induce the necrotic process well. Meanwhile, better LC in the HF-SRS group is generally considered to result from irradiation with higher BED. In addition to this point of view, we speculate that the acquisition of tumor cells radiosensitivity due to redistribution in the cell cycle and reoxygenation may play an important role in the local control of large BMs than expected [53, 54]. How large tumors can be safely and effectively treated using HF-SRS instead of surgical resection and whether HF-SRS will be more beneficial than SF-SRS even in small tumors remains unclear. Thus, the window of tumor size in which HF-SRS is helpful and the optimal dose per fraction and dose rate according to tumor size need to be established.

Meanwhile, as large peptide molecules such as monoclonal antibodies have recently been revealed to partially penetrate the blood–brain barrier in BM patients and exert tumor control effect, a combinational approach of SRS plus targeted or immunotherapy (TT/IT) has attracted attention [55].

Although data are limited and mostly retrospective, SRS may potentially synergistically affect LC and OS when combined with certain TT (in patients with EGFR-mutated NSCLC; HER 2-mutated breast cancer; and BRAF^{V600E}-mutated melanoma) or IT, compared to SRS alone [56–58]. ITs are profitable to patients lacking a driver mutation who do not benefit from novel targeted therapies. Regarding the optimal timing of IT treatment in BM patients, several studies demonstrated that concurrent administration of IT with SRS or immediately after SRS conferred better LC or OS than IT prior to SRS [58–60]. There are conflicting results in the toxicity issue of combining SRS with TT/IT in BM, with symptomatic RN and intra-tumor hemorrhage being increased especially those with melanoma [57, 61]. Unfortunately, the studies included in this review did not specify adjuvant therapies, including TT/IT, except the study conducted by Flannery and colleagues [27]. Therefore, it was not possible to compare the effects of TT/IT on the treatment outcomes of SF-SRS and HF-SRS. The synergistic pros and cons of SRS with TT/IT need to be compared between the HF-SRS and SF-SRS groups in the future.

Limitations

The tumor α/β ratio may vary with the pathology: 10–30 Gy for squamous cell cancer and 4–5 Gy for breast cancer [62]. However, the studies except one included in this review had mixed primary cancer pathologies, with lung cancer being the majority. Given the complexity of calculating the BED with different α/β according to pathology, we used an α/β of 10 as the representative value for metastatic brain tumors to conceptually compare the difference in BED between the SF-SRS and HF-SRS groups. Moreover, we estimated the BED based on a linear-quadratic model, which does not sufficiently represent the complexity of the underlying biology, although it is widely used. Whether the linear-quadratic model is applicable to estimate the BED in HF-SRS has not been verified. The time between fractions in HF-SRS may influence BED; however, we considered the effect of tumor proliferation during the short fractionation schedule to be imperceptible in general and did not reflect it in the BED calculation formula. Due to these limitations of BED estimation, it is necessary to be cautious when comparing BED between the SF-SRS and the HF-SRS groups.

Conclusions

Hypofractionation in SRS enables higher BED$_{10}$ administration to the target, resulting in better local control of large BMs, and simultaneously reduces radiation toxicity, compared to SF-SRS. Thus, HF-SRS should be considered a priority for SF-SRS in patients with large BMs who are not suitable to undergo surgical resection.

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