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CLINICAL STUDY

Five fraction stereotactic radiotherapy after brain metastasectomy: a single-institution experience and literature review

S. Rogers[1] · A. Stauffer[2] · N. Lomax[1] · S. Alonso[1] · B. Eberle[1] · S. Gomez Ordoñez[1] · T. Lazeroms[1] · E. Kessler[1] · M. Brendel[3] · L. Schwyzer[2] · O. Riesterer[1,4]

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Abstract

Purpose The outcomes of five fraction stereotactic radiotherapy (hfSRT) following brain metastasectomy were evaluated and compared with published series.

Methods 30 Gy in 5 fractions HfSRT prescribed to the surgical cavity was reduced to 25 Gy if the volume of 'brain−GTV' receiving 20 Gy exceeded 20 cm^3. Endpoints were local recurrence, nodular leptomeningeal recurrence, new brain metastases and radionecrosis. The literature was searched for reports of clinical and dosimetric outcomes following postoperative hfSRT in 3–5 fractions.

Results 39 patients with 40 surgical cavities were analyzed. Cavity local control rate at 1 year was 33/40 (82.5%). 3 local failures followed 30 Gy/5 fractions and 4 with 25 Gy/5 fractions. The incidence of leptomeningeal disease (LMD) was 7/40 (17.5%). No grade 3–4 toxicities, particularly no radionecrosis, were reported. The incidence of distant brain metastases was 15/40 (37.5%). The median overall survival was 15 months. Across 13 published series, the weighted mean local control was 83.1% (adjusted for sample size), the mean incidence of LMD was 14.9% (7–34%) and the mean rate of radionecrosis was 10.3% (0–20.6%).

Conclusion Postoperative hfSRT can be delivered with 25–30 Gy in 5 fractions with efficacy in excess of 82% and no significant toxicity when the dose to 'brain−GTV' does not exceed 20 cm^3.

Keywords Brain metastases · Postoperative · Resection · Stereotactic · Radiotherapy · Radiosurgery

Introduction

Resection of brain metastases (BM) is indicated to relieve raised intracranial pressure, to relieve symptoms that have not responded to steroid therapy and to acquire tissue for histological diagnosis [1]. Postoperative irradiation sterilizes residual microscopic disease and reduces local recurrence [2]. Postoperative whole brain radiotherapy (WBRT) was standard practice however is associated with neurocognitive impairment and a lack of survival benefit [3]. Analagous to primary radiosurgery, targeted irradiation of the surgical cavity has now been widely adopted. Postoperative stereotactic radiosurgery (SRS) following brain metastasectomy reduces local recurrence by 50% as compared with MRI-based follow-up [4] and is neuroprotective as compared with WBRT [3]. Therefore postoperative SRS has become a standard of care. This study presents the outcomes of a uniform series of patients treated with postoperative hfSRT according to a prospective standardized protocol to evaluate efficacy and toxicity. Similar published series were evaluated with the aim of guiding the future practice of postoperative hfSRT.

✉ S. Rogers
susanne.rogers@ksa.ch

1 Radiation Oncology Center KSA-KSB, Kantonsspital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland

2 Department of Neurosurgery, Kantonsspital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland

3 Department of Neuroradiology, Kantonsspital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland

4 Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Rämistrasse 100, 8091 Zurich, Switzerland

Methods

Patient selection and eligibility criteria

Consecutive patients who received postoperative hfSRT between 01/2016 and 02/2020 were identified from the institutional database. Up to three additional metastases were treated with primary SRS/hfSRT according to volume and location. Patients who had previously received WBRT, < 5 Gy per fraction, planning margins > 2 mm or who declined consent to participate were not included. Median interval between diagnosis on MRI and metastasectomy was 5.5 days (2–80 days).

Radiotherapy planning technique

A planning CT scan with 0.6 mm slice thickness in a custom-made radiosurgery mask (Brainlab, Germany) and a gadolinium-enhanced T1 MPR MRI (1 mm slice, no gap) were performed on the same day. Image fusion, autosegmentation and contouring of the surgical cavity were undertaken (Brainlab Elements). The CTV was the cavity with extension along the dura or sinus in case of preoperative contact and any residual tumor and was expanded by 2 mm to create the PTV [5]. Treatment planning used inversely optimized, modulated, non-coplanar arcs (Cranial SRS, Brainlab Elements) or VMAT (Eclipse, Varian, USA).

Dose prescription

30 Gray (Gy) in 5 fractions (biological equivalent dose (BED) for α/β ratios of 10 for tumor control (BED10 = 48 Gy) and of 2 for late effects (BED2 = 120 Gy)) was prescribed to 98–99% of the PTV, with maximum dose between 125 and 143% (equivalent to prescribing to the 70–80% isodose surface (%IDS) when normalized to the maximum point dose). The structure 'brain minus GTV' was created and if more than 20 cm^3 of this 'organ at risk' (OAR) received 20 Gy [6], the dose was reduced to 25 Gy in 5 fractions (BED10 = 37.5 Gy and BED2 = 87.5 Gy).

Treatment delivery

Treatment was delivered on alternate days with the Truebeam STx with Novalis Radiosurgery platform (Brainlab/Varian) with high definition MLC leaves (2.5 mm) without steroids unless SRS/hfSRT was delivered to intact metastases.

Outcome parameters

MRIs were performed 3-monthly and time to local recurrence, nodular leptomeningeal recurrence, new brain metastases and radionecrosis were calculated from the date of the last fraction of postoperative radiotherapy. Patient follow-up was censored at death or last follow-up until 05.04.2021.

Second-look radiology review

Given the overlap in appearance of tumour recurrence and radionecrosis and the potential for interobserver variability, MRIs reported to show local failure (LF) or nodular leptomeningeal disease (nLMD) underwent a 'second look' by a board-certified neuroradiologist. Features to differentiate recurrence from radionecrosis included new contrast enhancement in the surgical cavity, tumor progression in the case of residual tumor [7], low apparent diffusion coefficient (ADC) values [8] and ratio [9], 'lesion quotient' (ratio of maximal cross sectional area on T2 weighted to T1 weighted sequences) [10] as well as time elapsed following hfSRT [11].

Statistical analyses

Kaplan–Meier analysis was utilized to calculate the actuarial local control rate, otherwise descriptive statistics were applied. Ethics approval was granted (EKNZ 2091-01705).

Terms for the literature search in Pubmed with no time limit were "hypofractionated", "stereotactic", "radiotherapy", "radiosurgery", "metastasis", "adjuvant", "resection" and "surgery" and "brain" and a hand search of the references was performed.

Results

Patient characteristics

39 patients with 40 surgical cavities were eligible (Table 1). 5-ALA fluorescence was used to facilitate 'en bloc' resection and ultrasonic tissue ablation was used (CUSA, Integra Life Sciences, USA) where necessary. 97% of patients had a postoperative MRI within 24 h of surgery which showed suspected residual tumour in 10/40 cavities (25%). 100% of patients had a planning MRI within 6 days of radiotherapy. Median interval between resection and completion of hfSRT was 31 days (7–64 days). 22/40 (55%) cavities were treated with 30 Gy/5 fractions and 18/40 cavities (45%) received 25 Gy/5 fractions. The median follow-up was 11.7 months (2.7–40.1 months).

Treatment outcomes: local and leptomeningeal failure and toxicity

LF occurred in 7/40 cavities (17.5%) at a median time of 7 months (2.4–25.8 months), thus actuarial local control at last follow up was 82.5% (Fig. 1). Three patients with local

Table 1 Patient characteristics and treatment parameters

Variable	n (%) Total n = 30
Gender (M:F)	20:19
Karnofsky performance status	
Median	90
Range	(80–100)
Age (years)	
Median	62
Range	(17–81)
Histology	
Lung	
Adenocarcinoma	14
Non-adenocarcinoma	5
Breast	4
Renal	1
Melanoma	5
Gastroinstestinal	7
Colorectal	5
Oesophagus	1
Pancreas	1
Genitourinary	2
Sarcoma	1
Extracranial metastases	
Present/absent	28/12
Number of non-resected brain metastases per patient	
0	26
1	7
2	4
3	1
Location of brain metastases (lobe)	
Frontal	14
Parietal	6
Temporal	2
Occipital	5
Cerebellum	13
GTV	
Median	15.2
Range	1.4–31.9
PTV	
Median (cm^3)	25
Range	3.3–44.9
30 Gy	
Median (cm^3)	18.4
Range	3.3–31.5
25 Gy	
Median (cm^3)	37.6
Range	20.1–95.1
Dose (Gy) in five fractions	
30	20
25	19

failure had non-small cell lung cancer (NSCLC) and 4 had gastro-intestinal tumors (3 colorectal, 1 esophageal). Similarly, 7/40 cavities (17.5%), developed LMD at a median of 3 months (0.6–17.9), and 3/40 cavities developed both LF and LMD (Table 2), 1 following 30 Gy and two after 25 Gy in 5 fractions. The new contrast-enhancement which developed around the seven cavities was reported as recurrence rather than radionecrosis or postoperative change after independent re-evaluation. New brain metastases developed in 15/39 (39%) patients and median overall survival was 15 months (0.8–43.3 months).

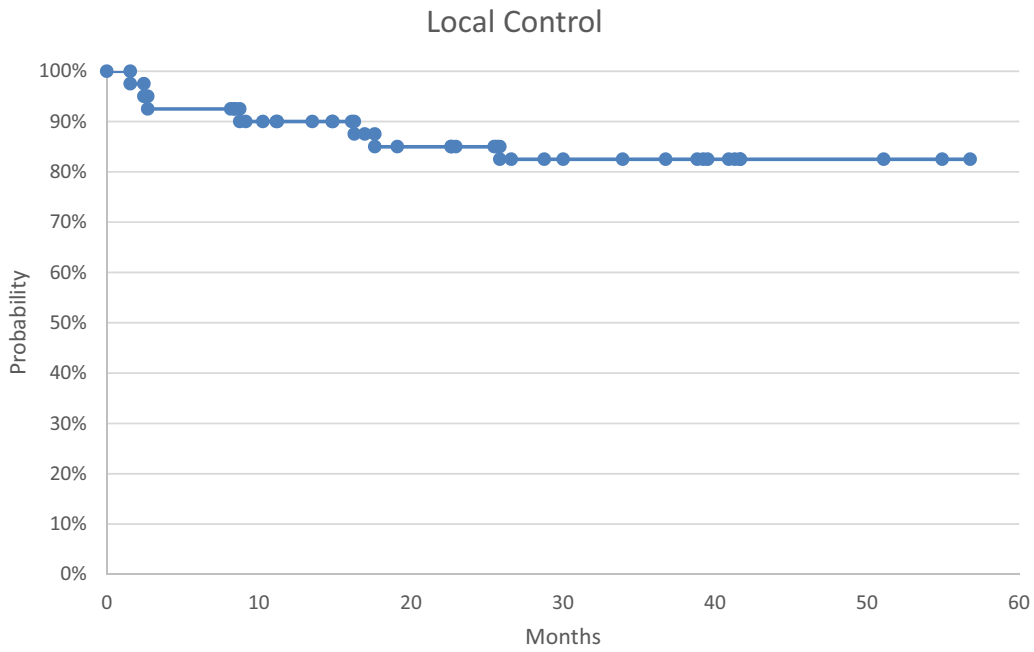
Of the ten patients with residual tumor, two developed a recurrence; one received 30 Gy, the other 25 Gy in 5 fractions. Of the eight patients with residual tumor who did not develop a local recurrence, three received 30 Gy and five received 25 Gy. Of those who developed nodular leptomeningeal recurrence (nLMD), 5 patients had NSCLC (3 adenocarcinoma, 2 non-adenocarcinoma), 1 had melanoma and 1 pancreatic adenocarcinoma. Of the three patients with both LF and nLMD, 2 had the large cell neuroendocrine adenocarcinoma subtype of NSCLC and the third had squamous cell lung cancer.

Data from the literature

The literature search identified 24 retrospective publications reporting hfSRT. Five that overlapped with others were excluded [12–16], as were series with multiple fractionation schedules. One series did not report details of the planning technique [17] and another presented outcomes at 6 months [18], thus 13 series were included. The 82.5% local control (LC) observed in the KSA series (Fig. 1) is similar to the weighted mean LC of 85.3% computed from the 13 published series (Table 3). However, we report a 0% incidence of radiological radionecrosis as compared with a mean of 10.3% (0–19%) radiological or histological radionecrosis. The 17.5% incidence of LMD in this series is comparable to the mean of 14.4% (7–34%) in the 13 publications.

Two additional series stating the volume of irradiated normal brain which resulted in histological or radiological radionecrosis (V xGy) following 5 fraction hfSRT were identified [13, 19]. Three data points were reported in a postoperative series [26] and two were derived in the setting of primary hfSRT [6, 19] applied to cavity hfSRT: [24] and this series. A plot of brain volume against dose in five fractions associated with radionecrosis yielded a linear inverse relationship, $R^2 = 0.59$ (Fig. 2).

From the literature, a PTV margin > 2–3 mm did not increase local control rate and the rate of radionecrosis was not higher with margins in excess of 3 mm (Supplementary Fig. 2), and there may be a higher incidence of radionecrosis with the 3 fraction schedules as compared with 5 fraction schedules (Supplementary Fig. 3).



Time (months)	0	10	20	30	40	50	60
Number of cavities at risk of local recurrence	40	37	35	33	33	33	33

Fig. 1 Kaplan–Meier analysis and risk table. An actuarial cavity local control rate of 82.5% at 12 months was achieved following 25–30 Gy in 5 fractions (D100%: V99%, Dmax 140%) with a 2 mm planning target margin

Table 2 Summary of characteristics of surgical cavities developing local failure or leptomeningeal relapse after hfSRT

	Local recurrence (n = 7)	Leptomeningeal relapse (n = 7)
Median PTV (cm^3)	28.3 (18.6–37.6)	29.2 (16.1–40.0)
Dose in five fractions (30/25 Gy)	3 (43%): 4 (57%)	4 (57%)/3 (43%)
Residual tumor postop (n = 10)	2 (20%)	2 (20%)
Cerebellum	3	2
Occipital	0	2
Frontal	2	1
Temporal	1	1
Parietal	1	1
Male:/female	5/2	4/3
Systemic therapy within 30 days	0	0
Surgical technique (en bloc vs ultrasonic aspiration)		3/2
Preoperative contact to dura (yes/no)		7/0

Table 3 Summary of 13 published series of patients treated with postoperative in 3 or 5 fractions with clinical outcome data

	No. of patients	No. of cavities	Average (prescribed) dose (Gy)	Average no. of fractions	Dose per fraction (Gy)	Prescription (%IDS)	BED 10	BED 2	PTV margin (mm)	Med PTV (cm^3)	Cavity local control at 1 year (%)	All lepto-meningeal disease at 1 year (%)	Radionecrosis (%) (MRI or histology)
Abuodeh [26]	75	77	25	5	5	NS	37.5	87.5	1–2	13.8 (1.93–128.43)	89		3
Combs [31]	159	159	32.5 (30–35)	5	6.5 (6–7)	95–100	53.6	138.1	3–4	25.9 (3.5–205.1)	75		4
Do [51]	30	33	25 (24–27.5)	5 (4–6)	5.5	80–90	33.8	93.8	2–3		82		
Eitz [32]	558	581	30	5	6	95–100[a]	48	120		23.9 (13.3–36.3)	84	13.3	8.6
Keller [40]	181	189	33	3	11	70	69.3	214.5	2	14.5	88	14.4	19
Lima [35]	26	26	25.5 (25–30)	5	5.2 (5–6)	80–90	37.6	91.8	2	19.8	84.7		
Minniti [27]	101	101	27	3	9	80–90	51.3	148.5	2	29.5	93		9
Minniti [28]	60	60	27	3	9	80–90	51.3	148.5	1	20.6	83		14
Minniti [33]	95	95	27	3	9	80	51.3	148.5	1	23	83	7	15
Steinmann [20]	11	11	32.5 (30–35)	5	6.5 (6–7)	NS	54.3	131.2	4	25.6	71		0
Vogel [30]	26	26	30	5	6	55–90	48	120	2–3	25.1	68.5	34	1
Navarria [41]	101	NS	30	3	10	NS	60	180	3	52.9	98.9	8.9	25.7
Garimall [42]	134	144	24	3	8	80–90%	43.2	120	3.5	28.2	92	12	11
Summary	Total 1751	Total 1812	Mean prescribed dose = 28.5 Gy	Mean no. fractions = 4.1	Mean dose per fraction = 6.8 Gy	Mean prescription isodose = 84%	Mean BED_{10} = 51.3	Mean BED_2 = 135.5	Mean PTV margin = 2.8 mm	Mean PTV = 25.9 cm^3	Median LC = 85.3% Weighted mean LC = 83.1%	Mean 1 year LMD = 14.9%	Mean 1 year RN = 10.3%
This series	39	40	27.5	5	5.5	70%	48	120	2	24.9	82.5	17	0

NS not stated

[a]NS and derived from data in Table 1

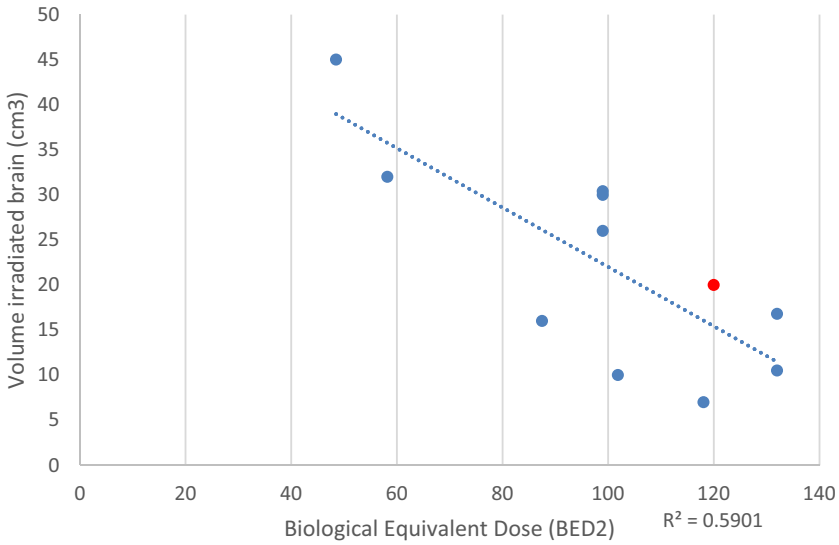


Fig. 2 Pooled toxicity data from 7 published series [5, 17–22] and the current series (red dot) show an inverse linear relationship between the volume of brain irradiated and the hfSRT dose to normal brain in 3–5 fractions reported to result in radionecrosis

Discussion

In the absence of published dose recommendations for 5 fraction postoperative hfSRT, we adopted those from a phase II trial published in the setting of primary hfSRT [6] as did another group who increased the fractionation to 10 × 4 Gy if more than 25 cm^3 of brain received more than 20 Gy [20]. They reported neither severe toxicity other than alopecia nor radionecrosis, however the LC rate at 1 year was only 71%. None of the other publications described their dose volume constraints, however several detailed the V xGy, which can represent total brain, 'brain−PTV' [13] or 'brain−GTV' [21]. Given the range of fractionation schemes, the 'radionecrosis dose' was converted to BED2 to enable comparison and the V xGy was plotted against the respective BED2 (Fig. 2). The line of best fit requires prospective validation but might form the basis for a future nomogram for the isotoxic prescription [22] of postoperative hfSRT.

A meta-analysis of 50 studies evaluated 3458 patients treated with SRS as well as hfSRT, yielding rates of cavity LC at 12 months of 83.7%, radionecrosis of 6.9% and LMD of 13% [23]. A review of predominantly postoperative SRS publications developed practice guidelines without recommended dose volume constraints [24] and a comprehensive review focusing on hfSRT again did not conclude with any recommendations. The aim of the current work was to compare and contrast with the most similar series, hence only the literature pertaining to postoperative hfSRT was included. None used an identical methodology but outcomes closely approximated those reported here.

Local control

The LC rate in this study was consistent with the median and weighted mean of the 13 published hfSRT series and the weighted mean LC of 83.7% across 50 SRS/hfSRT studies [23], where hfSRT achieved higher LC rates (87.3%) than SRS (80%) (p = 0.021) [23]. Unlike in the meta-analysis, in the current series prescribed dose from the 13 published and the current hfSRT series were converted to BED to allow comparison. As there does not appear to be a dose response above 5 × 6 Gy (Supplementary Fig. 1), and may well be an increase in radionecrosis above the corresponding BED2 of 120 Gy (Fig. 2), this endorses the 5 × 6 Gy schedule for postoperative hfSRT [17, 25].

Although intuitive that a higher dose might be needed to achieve local control in radioresistant histologies, only one series reported a correlation between histology and local control [26]. Further, better LC rates were reported with postoperative rather than primary hfSRT for melanoma [27] but not lung cancer brain metastases [28]. Consistent with Shi et al. [29], four of the seven patients who developed LF in this series had a GI primary tumor.

Common to many hfSRT series was an increase in fractionation with increasing cavity size [20], for example 3 × 8 Gy for 10–19.9 cm^3 and 5 × 6 Gy for 20–30 cm^3 [19, 30]. In the current series, the median PTV of cavities with recurrence approximated the median PTV for all 40 cavities but was indeed larger than the median PTV of the 33 without recurrence (Table 2). Reduction in cavity control rates have been reported for PTVs > 11.7 cm^3 [31], > 17 cm^3 [26] and > 23 cm^3 [32], however there was no such correlation when 3 × 8 Gy was increased to 5 × 6 Gy for PTVs > 20 cm^3 [18] as biological efficacy was maintained through fractionation [28, 30, 33–35].

Putative risk factors for local recurrence are residual tumor at the time of hfSRT and a prolonged interval between neurosurgery and radiotherapy. As 8 of 10 cavities with suspected residual tumor were controlled at 1 year, 5 × 5–6 Gy with Dmax 140% appears sufficient.

The aim in this series was to start hfSRT 30 days postoperatively. The median interval to start of hfSRT was 31 days but recurrence was not observed in the few patients who started after 60 days due to delayed wound healing or other patient factors. Similarly, a start more than 30 days postoperatively did not affect LC rates on meta-analysis [23].

Radionecrosis

Following observation that SRS plans with a lower conformity index (CI) were associated with better local control rates, a 2 mm rather than 0 mm planning margin has been recommended [5] however no benefit was shown on meta-analysis (LC 2 mm 84.3% vs 0 mm 83.1%, p = 0.71) [23]. A 2 mm margin in this series achieved LC rates equivalent to or in excess of series using 5 mm expansion (Supplementary Fig. 2) which does not support the need for larger margins and the consequent risk of radionecrosis [36]. The smaller margins and radiosurgical dose prescription employed in this series reduce the volume of irradiated normal brain and the dose reduction above 20 cm^3 of 'brain−GTV' to 20 Gy may also have been beneficial.

The maximum volumes of brain that can be safely irradiated with SRS have been identified [37, 38] and these data can be applied to hfSRT by calculating the single dose equivalent (SDE) [39], which has been reported to correlate with incidence of radionecrosis [29]. 3 × 7.4 Gy to the 70% isodose with Dmax 100%, daily was associated with a radionecrosis rate of 20% [32, 40]. 3 × 9 Gy (BED2 148.5 Gy) daily is associated with radionecrosis rates between 9 and 15% [27, 28, 33]. 10 Gy per fraction (BED2 = 180) achieved an 89.9% 1 year LC offset by a 25% incidence of radionecrosis [41]. The exception to the higher rates of radionecrosis with the three fraction schedule was 3 × 8 Gy daily to cavities > 3 cm diameter with only 2.9% incidence of radionecrosis [18]. This schedule equates to BED2 of 120 Gy, the same as 5 × 6 Gy without consideration of the overall treatment time. Symptomatic radionecrosis has been reported in patients treated with three rather than five fractions [42], matching our observations (Supplementary Fig. 3) and putatively due to the immunogenicity of this schedule [43].

On multivariate analysis, a V18 Gy in 3 fractions of 30–32 cm^3 normal brain was significantly associated with increased risk [27] and in an earlier evaluation, V24Gy in 3 fractions of 16.8 cm^3 was a significant predictor of radionecrosis [33]. 'Brain−GTV' used here and by others [44], is more conservative than 'brain−PTV' and may contribute to the lack of observed toxicity. The risk of radionecrosis reported in 36 of 50 studies was 6.9% and is generally thought to be acceptable [23].

Leptomeningeal recurrence

Nodular leptomeningeal disease (nLMD) is now recognized as a complication of brain metastasectomy [24, 45]. An incidence of 13% was calculated on meta-analysis [23] and factors such as larger cavities [32] and resection of multiple metastases may be risk factors [30] for tumor cell dissemination. More than 50 days between surgery and hfSRT has been reported to be associated with risk of LMD [30] as have breast histology and infratentorial location [46]. Breast cancer is commonly associated with classical LMD independent of neurosurgery [47] however, which might underlie the association with female gender in some reports. Three of seven patients with nLMD in this series had large cell neuroendocrine lung cancer, which may have a greater propensity to disseminate to the brain [48]. Piecemeal resection has also been linked to nodular LMD [49] and the 'en bloc' technique is preferred. Sterilisation of tumour cells dispersed in the cerebrospinal fluid at resection is the compelling rationale behind preoperative radiosurgery [50]. Ultimately, many of the factors influencing local recurrence and nLMD, such as dural contact [5], relate to the size of the metastasis.

Strengths and limitations

The strengths of this analysis are the uniform planning technique, protocol-based margins and dose prescription with delivery of image-guided hfSRT on an SRS platform. Contouring was performed by two experienced radiation oncologists previously shown to have only 5% interobserver variability (unpublished data) and MRI review was undertaken by a single neuro-radiologist. The weaknesses of the study are the mix of histologies, lack of histological confirmation of recurrence and that additional specialized imaging, such as metabolic imaging studies, was not performed because either WBRT was indicated or progression of extracranial disease prevented further investigation.

Our aim is efficacy with minimal toxicity and thus we currently favor 5 × 6 Gy even for small cavities as this achieves LC comparable to published series without toxicity other than grade 2 alopecia. Whether the dose should be reduced to 5 × 5 Gy for larger cavities remains unanswered, as the risk of radionecrosis may be three-fold less in the postoperative as opposed to the primary setting [44], but this approach did not compromise efficacy.

Conclusions

Postoperative hfSRT with 5 × 6 Gy (V99%: 100%, Dmax 140%) is an efficacious schedule without significant toxicity if the dose to 'brain−GTV' does not exceed 20 Gy to 20 cm^3. Prospective investigation of the dose volume constraints for

cavities exceeding this guidance is required to further optimize treatment regimens.

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Data availability The raw data will be made available upon reasonable request.

Declarations

Conflict of interest There are no conflicts of interest or competing interests. SR has received Speakers' Honoraria from Brainlab.

Ethical approval EKNZ 2091-01705.

Consent to participate Patients who declined consent for participation in clinical studies were not included.

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