International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Clinical Outcomes of Stereotactic Radiotherapy in Treatment of Patients with Oligometastatic Brain Tumor

Ehab Saad[1], Inas Abdou[1], Esraa Hanafy[2], Hussein Metwally[2]

[1] *Department of Clinical Oncology and Nuclear Medicine, Cairo University, Egypt*
[2] *Department of Clinical Oncology, Fayoum University, Egypt*

Abstract

Hypo-fractionated stereotactic radiotherapy (HFSRT) is now commonly utilized to treat oligometastatic brain tumors using volumetric modulated arc therapy (VMAT). We aimed to assess the effectiveness as well as the toxicity of hypo-fractionated stereotactic radiotherapy (HFSRT) in the oligometastatic setting. Sixty patients were treated by linear accelerator-based HFSRT. Target lesions received 30 Gray in 5 fractions. Radiological assessment by MRI was done 3 months after receiving the radiation, then every 3 months in the first year, and then every 6 months. Toxicity was evaluated using Radiation Therapy Oncology Group central nervous system toxicity criteria. The median overall survival was 15.2 months, and 71.7% of patients died at the last follow-up. The rate of complete response (CR), partial response (PR), no change (NC), and progressive disease (PD) were 40%, 25%, 20%, and 15% respectively. Local tumor control (LC) was 83.3% at 6 months, and 76.7% at 12 months. 49 patients (81%) reported at least one toxicity with different grades from I-III. Late side effects like neuro-cognitive disturbance grade I were reported in 8 patients only (13.3%). HFSRT is a safe and effective method for the treatment of oligometastatic brain tumors, with high local control rates.

Keywords: Stereotactic Radiotherapy, oligometastatic Brain Tumor, brain metastases.

Full length article **Corresponding Author*, e-mail: ehab.saad239@gmail.com

1. Introduction

Due to advancements in managing systemic disease, enhanced radiological detection, and increased survival rates, brain metastases (BMs) have become more prevalent than primary tumors in the brain in cancer patients. Brain metastases develop in around 20 to 40% of cancer patients and are an important factor impacting patient survival [1]. Brain metastases are commonly found in patients with lung, breast, and skin (melanoma) cancers, accounting for 67–80% of cases. Patients diagnosed with small cell lung cancer (SCLC) or non small cell lung cancer (NSCLC) are more likely to have brain metastases at the time of diagnosis, while patients with melanoma had the highest likelihood of having brain metastases when initially diagnosed. Prostate, head and neck, non-melanoma skin, and esophageal carcinomas rarely spread to the brain [2]. When evaluating the prognosis of brain metastatic patients in the clinical setting, various factors are considered, including age, performance status, number, size, and location of brain metastases, primary tumor control status, recursive partitioning analysis classes (RPA), and graded prognostic assessment index (GPA) [3]. Advanced management techniques were used for patients having brain metastases in clinical settings. Whole brain radiation therapy (WBRT) used to be the standard of care in treating brain metastases (BMs). Local treatments such as stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy (FSRT) are now preferred due to their higher efficacy and lower risk of side effects for patients with oligometastatic brain tumors measuring one to three cm and having five or fewer lesions [4]. SRS offers a high 12-month local control rate (range: 70% to 90%) and has lower toxicity profiles than WBRT. Moreover, SRS offers greater benefits for less severe injuries and a reduced chance of leptomeningeal spread compared to conventional surgery. The results from the Radiation Therapy Oncology Group (RTOG) 90-05 trial shows that Stereotactic Radiosurgery (SRS) provides 49% local control in brain metastases (BMs) ranging from 2.1 to 3 cm, and 45% in BMs measuring between 3.1 and 4.0 cm [5]. Fractionated stereotactic radiation treatment (FSRT) is utilized instead of single-fraction stereotactic radiosurgery (SRS) to enhance overall effectiveness of local radiotherapy. The ideal dosage fractionation for the treatment of BMs with FSRT has not been identified [6]. This study is a retrospective study examining overall effectiveness and

safety of fractionated stereotactic radiotherapy (FSRT) using volumetric modulated arc therapy (VMAT) in patients with oligometastatic brain tumors.

2. Materials and Methods

This retrospective study was conducted from January 2020 to December 2022. We performed a retrospective evaluation of the medical records of 60 patients with brain metastases of different primary histologies and were treated with FSRT.

2.1. Inclusion criteria

1. Patients are 20-80 years old.
2. WHO performance status: 0 or 1.
3. Patient with five or fewer brain metastases of a solid tumor.
4. Brain lesions measure between 5 and 30mm in diameter.
5. Patients with an extracranial control disease can be included if they have achieved a complete response, partial response, or stable disease for over 3 months following systemic therapy such as chemotherapy, immunotherapy, or targeted therapy.

The data were collected from the files regarding primary cancer, Karnofsky performance score (KPS), recursive partitioning analysis (RPA) classification at the time of FSRT ,graded prognostic assessment (GPA) score, lesions number treated, presence of extracranial metastases, date of death or last follow-up, and FSRT treatment records, including the assessment of the patients clinically and radiologically by MRI brain with consecutive intervals to assess response to treatment and evaluate the toxicity.

2.2. Radiotherapy technique for planning and treatment

The following steps were taken in the process of planning and delivering stereotactic irradiation:

1. Patients were simulated in the supine position with a thermoplastic mask used for immobilization.
2. Imaging (CT, MRI) was performed from the cranial vertex to the third cervical vertebra to localize and position, define the target volume and organs at risk (OAR), calculate, also create a 3D representation of the isodose distribution.
3. Treatment planning often involves a planned CT scan and a high-field 3D distortion-corrected T1 contrast MRI with gadolinium to accurately delineate tumor volumes. The area of contrast enhancement on a CT scan or MRI is known as the gross target volume (GTV). Treatment volumes do not include the surrounding edema. The planning tumor volume (PTV) is determined by including a 2 mm geometrical margin. The total dose prescribed was 30Gy/5fr/1w.Treatments were designed using the Eclipse treatment planning system by VMAT, and treatment was delivered using 6 MV beams from a linear accelerator. Patients were aligned daily using kV orthogonal radiographs and cone-beam CT (CBCT) to ensure accurate positioning before treatment.

2.3. Outcome evaluation

In this study, toxicity and local control are the primary objectives. Patients were followed up by history taking, neurological examination, and MRI brain scans at scheduled intervals (during the first year, every three months; after that, every six months) to check tumour status and the presence of symptoms. The first MRI is to be done 3 months after end of SBRT. After radiation necrosis has been excluded from serial MR imaging, local progression is defined as an increase in the enhancing abnormality beyond the irradiated volume. Distant failure is characterized by the emergence of newly found brain metastases or leptomeningeal enhancement beyond the area that received radiation. A "complete response" (CR) signifies the eradication of all target lesions. Partial response (PR) is a reduction of at least 30% in the total diameter of target lesions, whereas progressive disease (PD) is an increase of at least 20% in those diameters in comparison to the smallest diameters during therapy. Stable disease (SD) is characterized by a lack of significant changes that would meet the criteria for partial response (PR) or progressive disease (PD). Responses that are not progressive disease (CR, PR, and SD) are considered locally managed. The Common Toxicity Criteria for Adverse Events Version 4 (CTCAE v. 4) is used to score toxicities. Acute toxicity is determined three months after the start of therapy. The RTOG acute central nervous system (CNS) morbidity grading criteria is used to classify toxicities. The symptoms of acute toxicity included headaches, fatigue, nausea/vomiting, dizziness/imbalance, edema, motor neuropathy, sensory neuropathy, seizures, and neurocognitive impairment as described by the patients.

2.4. Statistical analysis

The data was gathered, organized, and statistically examined utilizing SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA). In qualitative data, absolute frequencies and relative frequencies were provided, while in quantitative data, the mean ± SD and median with range were displayed. Persons and Spearman's rank correlation coefficient were calculated to assess the relationship between various study variables, (+) sign indicates direct correlation, and the (-) sign indicates inverse correlation. Strong correlation is shown by values close to 1, and poor correlation is indicated by values close to 0. All tests were two-sided. Kaplan-Meier analysis was used in survival analysis. Cox-regression has been utilized to detect the predictors for overall survival in the studied group. P-values less than 0.05 were regarded as statistically significant (S), while those greater than 0.05 were regarded as statistically insignificant (NS).

3. Results and discussion

3.1. Patient Clinical and Treatment Characteristics

The patients' age ranged from 21 to 80 years, with the mean age of the cases being 54.17±13.70 years. 35 patients (58.3%) were males, and 25 patients (41.7%) were female. Regarding BMS number, 73.3 percent of the cases had a single brain metastasis, 18.3% of cases had two brain metastases, and 8.3% had three brain metastases. 75% of cases showed KPS grade 100%, KPS grade 90% was found in 20% of cases, and 5% of cases showed KPS grade 80%. The origin of 40% of tumors was non-small cell lung cancer (NSCLC), 33.3% were breast cancer, 8.3% were renal cell carcinoma (RCC), 6.7% were soft tissue sarcomas (STS), and 3.3% were colorectal cancer. Our results demonstrated that 70% of tumors were adenocarcinoma, 10% had squamous cell cancer (SCC), 8.3% had renal cell carcinoma (RCC), while 11.7% had other pathologies (Table 1). The mean planning target volume size was 23.04±16.2 with a median 18.55cc (12-27.6), with 50% of the PTV size above 18.5 cc.

3.2. Local control

Regarding local control through 3 months, 40% of cases showed a complete response, 25% showed a partial response, 20% reported a stationary disease, and 15% of cases showed progressive disease. Local tumor control rates were 83.3% after six months, 76.7% after 12 months, 67.2% after 18 months, and 37% after 24 months. With six patients lost follow up at the end of our study (Table 2).

3.3. Toxicity

A total of 49 patients (81%) had side effects of different grades of toxicity, and the rest of the patients, 11 (18%), were free. 55% of cases suffered from headache (48.3%) in grade 1, (5%) in grade 2, and (1.7%) in grade 3. About 38.3% of cases suffered from nausea, (15%) were in grade 1, (21.7%) were in grade 2, and (1.7%) were in grade 3. In addition, 35% of cases suffered from vomiting, 26.7% were in grade 1 and 8.3% were in grade 2. In addition, fatigue was reported in 31.7% of cases, with 25% being grade 1 and 6.7% being grade 2. While 13.3% of cases suffered from seizures, 6.7% were in grades 1 and 2. About 16.7% of cases showed depression grade 1, and worse toxic effects like neuro-cognitive disturbance grade 1 were reported in 8 patients (13.3%). (Table 3). Regarding recursive partitioning analysis, most cases (73.3%) were RPA class 1 and (26.7%) were class 2. Regarding graded prognostic assessment, 38.3% of patients scored 0.5, 35% scored 0, and 26.7% scored 1.

3.4. Overall survival

71.7% of cases died and only 28.3% survived at the time of data analysis. Age group and mean survival time showed a statistically significant correlation, where patients under the age of 55 showed a significantly longer survival estimate. There is a statistically significant correlation between average survival time and RPA. With a p-value of less than 0.001, patients in RPA class 1 had a significantly longer predicted survival time. A statistically significant difference was seen between GPA and mean survival time. Patients with scores of 0.5 and 1 showed significantly longer survival ($p<0.001$*). The mean survival time and local control at three months were found to have statistically significant correlation. Cases that had progression at 3 months had a considerably lower mean survival time. (Table 4), (Figure 1). There was a significant positive correlation between GPA and overall survival duration, while there was a significant negative association with age, the number of metastases, PTV size, RPA, and overall survival duration. (Table 5) .Although FSRT has shown a high LC rate and fewer side effects compared to the other lines in brain metastasis management, there are no specific guidelines for dose and fractionation owing to several parameters such as the type of primary tumor, PTV size, and BMs number [7]. Sixty patients were included in this retrospective analysis and received a dose of 30 Gray in 5 fractions using VMAT. The biological effective dose (BED) of HFSRT was 48Gy, based on an α/β of 10Gy for brain metastasis. Our results have been recorded three months after the end of radiotherapy, as follows: 40% of cases showed CR, 25% of cases showed PR, 20% reported NC, and 15% of cases showed PD. LC was 83.3% after 6 months, 76.7% after 12 months, 67.2% after 18 months, and 37% after 24 months.

3.5. Efficacy of SRS versus HFSRT

Few datasets exist that compare schemas with one fraction versus those with multiple fractions. We still don't know the optimal fractional schemas and doses. Maxime et al. retrospectively assessed 179 patients, having one to three brain metastases. The patients received either SRS (14 Gray in a single fraction) or HFSRT (23.1 Gray in 3 fractions of 7.7 Gray on days 1, 3, and 5). Local control rates were 87.6% and 78.4% in the HFSRT group and 94% and 88.1% in the SRS group at 6 and 12 months, respectively. The difference in rates was not statistically significant ($p = 0.06$). It is worth noting that the GTV and PTV volumes were notably lower among the SRS cohort. In comparison to the SRS group, the BED10 was 18% higher compared to the HFSRT group, with values of 41 Gy10 and 33.6 Gy10, respectively. There was no statistically significant variation in local control among the SRS and HFSRT cohorts. One lesion among the SRS cohort and nine among the HFSRT cohort developed brain radionecrosis [8]. In a systematic review, eleven papers were examined to investigate the dose-effect relationship. The prescribed isodose lines, GTV-PTV margins, and doses varied greatly between the trials; however, the LC rates were comparable in the SRS and HFSRT groups. When BED increased, the dose-response curve between LC and BED showed greater efficacy. At least a 40 Gy BED12 was associated with an LC rate of 70% or more [9]. In an interesting BED-based SRT strategy, Matsuyama et al. reported that BED10 of around 80 Gy was used in HFSRT to treat 573 tiny brain metastases from NSCLC, regardless of the multi-fraction schemas utilized. Having a median PTV volume of 1.4 cc, they discovered 96.3% and 94.5% LC rates at 6 and 12 months respectively [9].

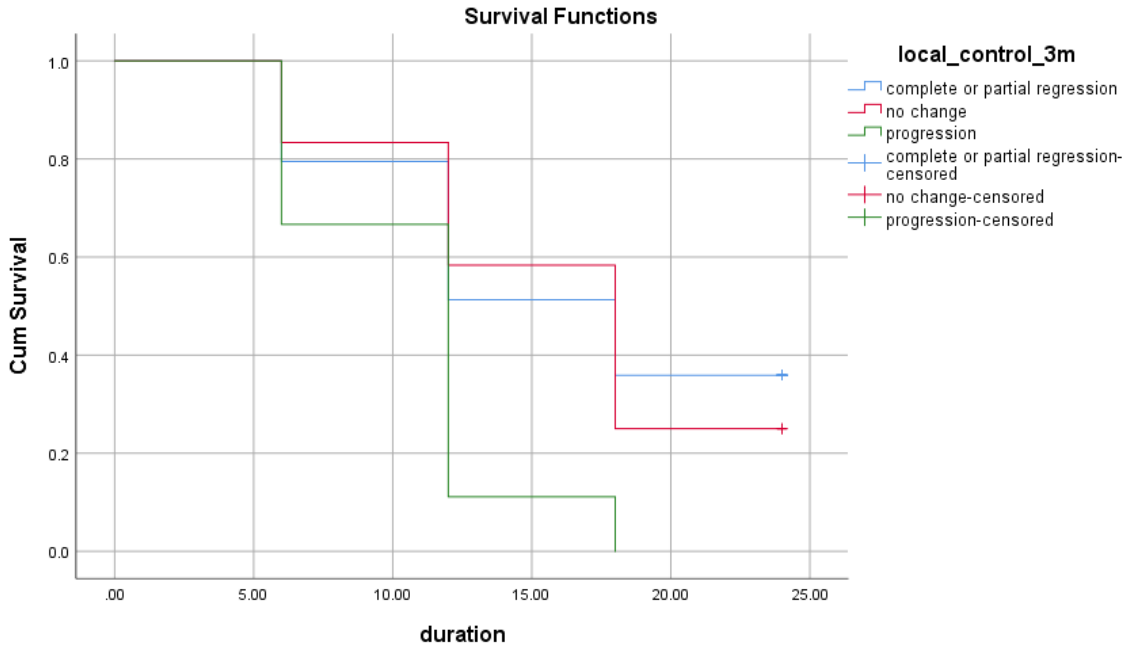

Figure 1. Kaplan-Meier of the association of local control for 3 months and Survival Time within the studied patients (n=60)

Table 1. The tumor characteristics of the studied patients (n=60)

Characteristic	Category	Study group (n=60)	
		No.	%
Tumor origin	NSCLC	24	40
	Breast cancer	20	33.3
	RCC	5	8.3
	CRC	2	3.3
	STS	4	6.7
	Others	5	8.3
Tumor pathology	Adenocarcinoma	42	70
	SCC	6	10
	RCC	5	8.3
	Others	7	11.7

Table 2. Local control and progression probability of the studied patients (n=60)

Characteristic	Category	Study group (n=60)	
		No.	%
Local control 3 months	complete response	24	40
	partial response	15	25
	Stationary disease	12	20
	progressive disease	9	15
progression 6ms	No	50	83.3
	Yes	10	16.7
progression 12ms	No	46	76.7
	Yes	14	23.3
progression 18ms	No	39	67.2
	Yes	19	32.8
progression 24ms	No	20	37
	Yes	34	63

Table 3. Toxicity of the studied patients (n=60)

Characteristic	Category	Study group (n=60)	
		No.	%
Headache	**No**	27	45
	Grade 1	29	48.3
	Grade 2	3	5
	Grade 3	1	1.7
Nausea	**No**	37	61.7
	Grade 1	9	15
	Grade 2	13	21.7
	Grade 3	1	1.7
Vomiting	**No**	39	65
	Grade 1	16	26.7
	Grade 2	5	8.3
Fatigue	**No**	41	68.3
	Grade 1	15	25
	Grade 2	4	6.7
Seizure	**No**	52	86.7
	Grade 1	4	6.7
	Grade 2	4	6.7
Depression	**No**	50	83.3
	Grade 1	10	16.7
Neuro-Cognitive disturbance	**No**	52	86.7
	Grade 1	8	13.3

Table 4. Kaplan-Meier of the association of Local control for 3 months and Survival Time within the studied patients (n=60)

Local control	Mean				Chi square	P value
	Estimate	Std. Error	95% Confidence Interval			
			Lower Bound	Upper Bound		
complete or partial regression	16.000	1.116	13.812	18.188	6.373	**0.04***
No change	16.000	1.780	12.512	19.488		
Progression	10.667	1.333	8.053	13.280		

Table 5. Correlation between different parameters and overall survival duration of the studied patients

Parameters		Overall survival duration
Age	R	-0.636**
	P value	0.000
	N	60
BMs number	R	-0.266*
	P value	0.040
	N	60
PTV size cc	R	-0.298*
	P value	0.021
	N	60
RPA	R	-0.659**
	P value	0.000
	N	60
GPA	R	0.796**
	P value	0.000
	N	60

Emmanouil et al. retrospectively evaluated and compared the toxicity profiles and the efficacy of SRS and FSRT. They treated 260 patients having one to three BMs with either SRS (the median dosage: 20 Gray; n = 138) or one of the two HFSRT dose regimens: 7 × 5 Gray (n = 61) or 10 × 4 Gray (n = 61). The response rates for SRS, 7 × 5 Gy, and 10 × 4 Gy were 89%, 92%, and 90%, respectively. As a result, the two FSRT schemes that were employed had BEDs that were comparatively good [10]. Dario Di Perri et al. published a retrospective single-center analysis of HFSRT for brain metastases using three distinct dosage regimens (i.e., 27 Gray in 3 parts, 30 Gray in 5 sessions, and 35 Gray in 5 sessions). BED is 48 Gy, 51.3 Gy, and 59.5 Gy, respectively, assuming an alpha/beta ratio of 10 Gy. Given that the lesions treated with 30 Gy/5# had a lower BED and were greater in size than lesions treated with 27 Gy/3#, the local control was worse for the former (p = 0.02), with 12-month local failure rates of 42.7% and 20.4%, respectively. With a 12-month local failure rate of 37.5%, local control after 35 Gy/5# didn't differ significantly from 27 Gy/3# (p-value= 0.19) or from 30 Gy/5# (p-value= 0.49) [11].

3.6. Survival analysis

In our study, forty-three (71.7%) patients had died at the last visit of follow up. The median survival time was 15.2 months. There was a significant difference statistically between GPA score 0.5 and score 1 and mean survival time (p<0.001). GPA was the most significant predictor of survival among patients having brain metastases. According to the findings from Emmanouil et al.'s publication, which detailed a retrospective evaluation and comparison of the toxicity and efficacy profiles of SRS and FSRT for the treatment of 260 patients with BMs, the cohort's median OS time was 9 months, divided into three groups: 8 months for SRS, 7 months for 7 × 5 Gray, and 10 months for 10 × 4 Gray (p-value of 0.575). For the SRS group, the 1-year local PFS was 73%; for the 7 × 5 Gray group, it was 75%; and for the 10 × 4 Gray group, it was 71% (p-value of 0.191). A multivariate analysis revealed that RPA class I was statistically significant for improved survival [10]. Samuel R. et al. documented the survival rate of 72 patients treated by FSRT who received 25 or 30 Gray in 5 fractions. Five months was the median follow-up period (range: 1-71 months). With an estimated 6- and 12-month OS of 63% and 29%, respectively, the median OS was 7 months [12]. An analysis of 36 individuals who had HSRT for 52 brain metastases was published by Alexander K. et al. Of these 52 lesions, 7 were treated by HSRT being the main treatment, while 45 were treated with whole-brain radiation in addition to a boost. The recommended dose range was from 20 to 36 Gy, with a dose of 25 Gy as the median. With a range of 0.9 months to 26.8 months, the median follow-up period was 6.6 months. 10.8 months was the median OS time [13]. The discrepancy in survival rate among the previous studies can be explained by the heterogeneity of several factors, like different age groups, KPS, primary tumors and different doses of stereotactic radiotherapy.

3.7. Toxicity analysis

As regards toxicity in our study, 49 patients (81%) reported at least one side effect with a different grade from I to II. The most common symptoms were headache, vomiting, and fatigue, where 33 cases (55%) reported grades 1-3 headache, 21 cases (38.3%) reported grades I-II vomiting and 19 cases (31.7%) reported grades I-II fatigue. Two cases only reported grade III headache and nausea. Late side effects like neuro-cognitive disturbance grade I were reported in only 8 patients (13.3%), with only two patients had documented radionecrosis (RN). When comparing our findings to those of a single-center retrospective research using HFSRT for brain metastases, Dario Di Perri et al. reported that 33 (9.2%) of the lesions had RN. The annual RN rate was 8.8% in total. First, as both previous regimens offer greater BED, risk was increased in lesions getting 27 Gy in 3# ($p = 0.03$) compared to lesions receiving 35 Gy in 5# ($p < 0.01$) than in lesions receiving 30 Gy/5#. Secondly, patients who was treated with immunotherapy within three months after HFSRT had a greater risk ($p = 0.03$) than those who did not [11]. Similar to the previous study, Emmanouil Fokas et al, documented that FSRT has less toxicity effects when compared to SRS due to differences between their BED. Grade III acute toxicities (vomiting, nausea and headache) affected 3, 0 and 0% of patients in the SRS, 7 × 5 Gy and 10 × 4 Gy cohorts, respectively. In terms of long-term adverse effects, 6% of SRS patients had grade III chronic toxicities, which include headaches, alopecia, motor, neurocognitive, and visual or auditory impairment; 2% of the 7 × 5 Gray group and 1% of the 10 × 4 Gray group also had these toxicities. Overall, compared to the 7 × 5 Gray and 10 × 4 Gray regimens, SRS has been associated with increased risk of (grades I–III) toxicity (14 vs. 6 vs. 2%, respectively; p-value of 0.01) [14]. The total volume of the normal brain receiving 24 Gy (V24), 21 Gy (V21), and 18 Gy (V18) was found to be predictive of RN by Giuseppe Minniti et al. when using HFSRT (three fractions) to treat intact metastases or excision cavities. Exceeding these cutoffs resulted in an increased incidence of RN: V24 ≥ 16.8 cc, V21 ≥ 20.9 cc, and V18 ≥ 26.2 cc, or ≥ 30.2 cc [15]. Faruqi et al. reported that a bigger V30 brain volume was associated with an increased risk of unfavorable radiation effects in intact metastases treated with 5 fractions of HFSRT, with a median dose of 30 Gy (range 20-35 Gy). When the volume of brain tissue receiving a radiation dose of more than 30 Gy (V30) exceeded 10.5 cubic centimeters, 61% of the targets developed symptomatic necrosis after one year [16].

4. Conclusions

Our results confirmed that HFSRT is both safe and effective in the management of oligometastatic brain metastasis, with an acceptable toxicity profile. Several studies in the literature have suggested the employment of HFSRT over SRS due to its greater local control and fewer adverse effects. This is probably due to the potential radiobiological advantage of HFSRT, which allows for a higher biologically effective dose (BED). However, due to the wide range of previously prescribed doses of HFSRT, we recommend further prospective comparative studies between different dose regimens with a large sample size to identify the ideal dose regimen for HFSRT regarding local control and toxicity.

References

[1] X. Lin, L.M. DeAngelis. (2015). Treatment of brain metastases. Journal of clinical oncology. 33 (30) 3475.

[2] A. Lauko, Y. Rauf, M.S. Ahluwalia. (2020). Medical management of brain metastases. Neuro-Oncology Advances. 2 (1) vdaa015.

[3] C.X. Sun, T. Li, X. Zheng, J.F. Cai, X.L. Meng, H.J. Yang, Z. Wang. (2011). Recursive partitioning analysis classification and graded prognostic assessment for non-small cell lung cancer patients with brain metastasis: a retrospective cohort study. Chinese Journal of Cancer Research. 23 177-182.

[4] C.G. Patil, K. Pricola, J.M. Sarmiento, S.K. Garg, A. Bryant, K.L. Black. (2017). Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database of Systematic Reviews. (9).

[5] C. Zhou, Y. Xia, P. Huang, L. Guan, X. Shen, D. Hao, H. Yin. (2020). Fractionated stereotactic radiation therapy using volumetric modulated arc therapy in patients with solitary brain metastases. BioMed Research International, 2020.

[6] S. Baliga, M.K. Garg, J. Fox, S. Kalnicki, P.A. Lasala, M.R. Welch, N. Ohri. (2017). Fractionated stereotactic radiation therapy for brain metastases: a systematic review with tumour control probability modelling. The British journal of radiology. 90 (1070) 20160666.

[7] K.A. Eitz, S.S. Lo, H. Soliman, A. Sahgal, A. Theriault, M.B. Pinkham, S.E. Combs. (2020). Multi-institutional analysis of prognostic factors and outcomes after hypofractionated stereotactic radiotherapy to the resection cavity in patients with brain metastases. JAMA oncology. 6 (12) 1901-1909.

[8] M. Loo, Y. Pin, A. Thierry, J.B. Clavier. (2020). Single-fraction radiosurgery versus fractionated stereotactic radiotherapy in patients with brain metastases: a comparative study. Clinical & experimental metastasis. 37 425-434.

[9] M. Loo, J.B. Clavier, J. Attal Khalifa, E. Moyal, J. Khalifa. (2021). Dose-response effect and dose-toxicity in stereotactic radiotherapy for brain metastases: a review. Cancers. 13 (23) 6086.

[10] E. Fokas, M. Henzel, G. Surber, G. Kleinert, K. Hamm, R. Engenhart-Cabillic. (2012). Stereotactic radiosurgery and fractionated stereotactic radiotherapy: comparison of efficacy and toxicity in 260 patients with brain metastases. Journal of neuro-oncology. 109 91-98.

[11] D. Di Perri, R. Tanguy, C. Malet, A. Robert, M.P. Sunyach. (2020). Risk of radiation necrosis after hypofractionated stereotactic radiotherapy (HFSRT) for brain metastases: a single center

retrospective study. Journal of neuro-oncology. 149 447-453.

[12] S.R. Marcrom, A.M. McDonald, J.W. Thompson, R.A. Popple, K.O. Riley, J.M. Markert, J.B. Fiveash. (2017). Fractionated stereotactic radiation therapy for intact brain metastases. Advances in radiation oncology. 2 (4) 564-571.

[13] A.K. Kwon, S.J. DiBiase, B. Wang, S.L. Hughes, B. Milcarek, Y. Zhu. (2009). Hypofractionated stereotactic radiotherapy for the treatment of brain metastases. Cancer: Interdisciplinary International Journal of the American Cancer Society. 115 (4) 890-898.

[14] F. Putz, T. Weissmann, D. Oft, M.A. Schmidt, J. Roesch, H. Siavooshhaghighi, R. Fietkau. (2020). FSRT vs. SRS in brain metastases—differences in local control and radiation necrosis—a volumetric study. Frontiers in Oncology. 10 559193.

[15] G. Minniti, C. Scaringi, G. Lanzetta, D. Anzellini, F. Bianciardi, B. Tolu, S. Paolini. (2019). Comparative effectiveness of multi-fraction stereotactic radiosurgery for surgically resected or intact large brain metastases from non-small-cell lung cancer (NSCLC). Lung Cancer. 132 119-125.

[16] S. Faruqi, M. Ruschin, H. Soliman, S. Myrehaug, K.L. Zeng, Z. Husain, A. Sahgal. (2020). Adverse radiation effect after hypofractionated stereotactic radiosurgery in 5 daily fractions for surgical cavities and intact brain metastases. International Journal of Radiation Oncology* Biology* Physics. 106 (4) 772-779.