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RESEARCH ARTICLE **OPEN ACCESS**

SINGLE VS MULTIFRACTION RADIOSURGERY IN BRAIN METASTASES: A MONOISTITUTIONAL EXPERIENCE

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ABSTRACT

Stereotactic radiosurgery (SRS) has revolutionized the initial management of patients with brain metastases. It delivers focused, highly conformal, ionizing radiation to a target delineated using high-resolution imaging with minimal toxicity to adjacent brain structures. The most common late-delayed radiation effect of SRS is the development of brain radionecrosis (RN), which is often associated with the presence of different degrees of neurologic deficits. MF-SRS (2-5 fractions) has been used as an alternative to SF-SRS, with the aim to reduce the incidence of late radiation induced toxicity while maintaining high LC rates. The aim of this retrospective study was to evaluate the acute toxicity, local control, PFS, OS and incidence of RN in patients who received SF-SRS or MF-SRS for brain metastases. In this mono-institutional analysis, ninety consecutive patients with one or two brain metastases treated with SF or MF-SRS, were included. Endpoints of the analysis were radiation-induced brain necrosis and local control (LC), progression-free survival (PFS) in SF and MF-SRS. 90 patients were eligible and treated with SRS from June 2017 to June 2020 and retrospectively analyzed. 63 patients had lung cancer, 18 breast cancer, 5 renal cancer and 4 other cancer. Metastases were treated with Linac based radiotherapy, using VMAT technique. A total of 98 lesions were treated: 82 patients had single metastasis, while 8 patients had two metastases. Patients' median age was 65 years (range 40-80). Median follow up was 20 months (range 8-36 months). Patients were divided into two groups. Group A (35 patients) received a single fraction with a dose ranged from 21 Gy to 24 Gy; Group B (55 patients) received 3 fractions with a dose ranged from 24 Gy to 27 Gy. Size limits were metastases <2cm in longest diameter, largest tumor <4 ml in volume. 6 patients (7%) experienced toxicity grade 1 on the RTOG scale, consistent with minor neurological findings, such as headache but with ability to carry out normal activity without medication. 2 patients (2%) experienced toxicity grade 2 requiring home care and medication, including steroids. Every patient undergoing to perfusion and spectroscopic MRI before SRS and then every 3 months. At first follow up (3 months) 70% of patients had CR and 30% had SD, no PD. The 1-year local control rates were 80% in the SF-SRS group and 92.7% in the MF-SRS group. The 1-year PFS cumulative rate was 85.7%, 83.3% in the group A and 87% in the group B. The 1-year OS cumulative rate was 54.4%, while 51.4% in the group A and 56.4% in the group B. 7 patients (20%) undergoing SF-SRS and 5 (9%) subjected to MF-SRS experienced brain RN; the 1-year incidence rate of RB was 16.6% and 6.4%, respectively. MF-SRS at a dose of 27 Gy or 24 Gy in 3 daily fractions seems to be an effective and safety treatment modality for brain metastases, associated with better local control and a reduced risk of radiation-induced RN as compared with SF-SRS at dose ranged from 21 Gy to 24 Gy.

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INTRODUCTION

Brain metastases (BM) are the most common intracranial tumors in adults, occurring in 10–40% of cancer patients (1). The frequency of Brain Metastases appears to be rising as the result of an aging population, the improved neuroimaging (magnetic resonance imaging-MRI with spectroscopy, arterial spin labelling diffusion, and perfusion-weighted imaging), and the better treatment of systemic disease (1–3). The estimated median survival for patients with BM is 4–6 months (4). The ideal management of patients with BM is controversial, with alternatives as surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS). Stereotactic radiosurgery (SRS) has revolutionized the initial management of patients

with brain metastases (5-7). It delivers focused, highly conformal, ionizing radiation to a target delineated using high-resolution imaging with minimal toxicity to adjacent brain structures (8). The most common late-delayed radiation effect of SRS is the development of brain radionecrosis (RN), which is often associated with the presence of different degrees of neurologic deficits (9-10). MF-SRS (2-5 fractions) has been used as an alternative to SF-SRS (single fraction), with the aim to reduce the incidence of late radiation induced toxicity while maintaining high Local Control (LC) rates (11-14). The aim of this retrospective study was to evaluate the acute toxicity, local control and incidence of RN in patients who received SF-SRS or MF-SRS for brain metastases.

Radiobiological principles of SRS: A SRS dose of 20Gy delivered in 1 fraction is substantially more than the biologically equivalent dose (BED) of a commonly prescribed WBRT dose of 30Gy in 10 fractions. However, the greater BED alone may not explain the superior control and response rates inherent to SRS. It is postulated that additional biologic factors or cellular pathways specific to high dose per fraction radiation may be involved in the pathophysiology of SRS response. In particular, activation of the acid sphingomyelinase pathway has been shown to occur only when the dose per fraction increases beyond 8 Gy, and serves to activate tumor endothelial cell apoptosis, disrupt the tumor vasculature and increase tumor cell death (15). In addition, release of tumor-specific antigens leading to the priming of CD8+ T cells and a subsequent immune mediated response may further enhance tumor cell death again specific to SRS dosing (16). The radiobiology specific to SRS is an area of active research (17-18).

MATERIAL AND METHODS

In this mono-institutional analysis, the records of patients with BM treated at our institution between June 2017 and June 2020 were selected. We included patients who didn't received WBRT and surgical resection before the start of the study. Patients were selected for SF-SRS or MF-SRS according to size and proximity to critical organs (brain stem, optic pathway, or cranial nerves). Size limits were metastases <2cm in longest diameter, largest tumor <4 ml in volume. If patients were suitable for SF-SRS, healthy brain tissue volume receiving 12 Gy did not exceed 10 cc (19). The range of SF-SRS doses used was 21-24 Gy. Dose prescriptions in patients undergoing to MF-SRS were 3 × 8 Gy (total dose 24 Gy) or 3 × 9 Gy (total dose 27 Gy). For planning, computed tomography (CT) images of 1.25 mm thickness of the head immobilized in a tight thermoplastic stereotactic mask were obtained. All patients were treated with linear accelerator based SRS using the IPlan treatment planning system (Pinnacle). Every patient undergoing to perfusion, diffusion and spectroscopic MRI before SRS and then every 3 months. In each patient the gross tumor volume (GTV) was delineated using postcontrast slice (2-mm) gadolinium-enhanced T1/T2-weighted axial MRI sequences with 3D reconstruction, fused with planning computed tomography (CT) scans. The clinical tumor volume (CTV) was a zero-margin-expansion of the GTV. A 2-3 mm isotropic margin was added to GTV/CTV to generate the planning target volume (PTV). Using the linear-quadratic model for the estimation of dose-effect relationship adjusted for high doses (20), the biological effective dose (BED) of MF-SRS at doses of 27 Gy in 3 fractions was 40 Gy assuming an α/β of 12 Gy for brain metastases (BED12), corresponding to a single dose of approximately 22 Gy. To minimize damage to the surrounding tissues, planes not deviating from the RTOG protocol of conformity index (CI), quality of coverage, and homogeneity index (HI) were used (21). Cone Beam Computed tomographic imaging (CBCT) was used for setup verification before each fraction. Toxicity, neurological status and severity of complications were evaluated according to Radiation Therapy Oncology Group (RTOG) central nervous system toxicity criteria (22).

Follow-up was scheduled every 3 months with brain MRI. Complete responses were defined as total radiographic disappearance of lesion, while partial responses were defined as decrease in tumor volume >50%. Tumor progression was defined as any increase of tumor on contrast-enhanced T1-weighted images in at least 2 subsequent MRI studies associated with a cerebral blood volume (CBV) ratio>2.0 at dynamic susceptibility-weighted contrast-enhanced perfusion images (calculated for each lesion by dividing the tumor CBV by the mean CBV value of normal white matter). Stable or shrinking lesions over a 6-month period associated with a CBV ratio <2.0 were diagnosed as RN. (23). Distant failure was defined by the presence of new brain metastases outside the PTV. Endpoints of the analysis were acute toxicities, radiation-induced brain necrosis (RN), Local Control (LC), Progression-free survival (PFS) and Overall Survival (OS) in SF and MF-SRS.

RESULTS

Patient's characteristics: Ninety consecutive patients with one or two brain metastases treated with SF or MF-SRS, were eligible and retrospectively analyzed. 63 patients had lung cancer, 18 breast cancer, 5 renal cancer and 4 other cancer. Metastases were treated with Linac based radiotherapy, using VMAT technique. A total of 98 lesions were treated: 82 patients had single metastasis, while 8 patients had two metastases. Patients' median age was 65 years (range 40-80). Median follow up was 20 months (range 8-36 months). 25 patients had a Karnofsky performance status (KPS) score between 60-70, while 65 patients had a KPS score between 80-100. Patients were divided into two groups. Group A (35 patients) received a single fraction with a dose ranged from 21 Gy to 24 Gy; Group B (55 patients) received 3 fractions with a dose ranged from 24 Gy to 27 Gy. Group A was composed of lesions with diameter range of 0.6-1.4cm; Group B was composed of lesions with diameter range 0.6-2cm. TAB 1

Toxicities: 6 patients (7%) experienced toxicity grade 1 on the RTOG scale, consistent with minor neurological findings, such as headache but with ability to carry out normal activity without medication. 2 patients (2%) experienced toxicity grade 2 requiring home care and medication, including steroids. No patient developed a grade 3-4 toxicity. There was no statistically significant difference between the two groups in term of toxicities.

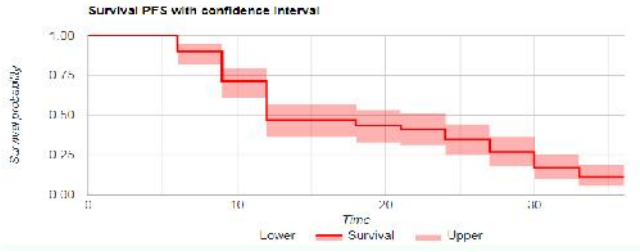
Local Control: At first follow up (3 months) 70% of patients (63 patients) had Complete Response (CR) and 30% (27 patients) had Stable Disease (SD), no patient showed Progression Disease (PD). At first follow up, Local Control was 100%.

Table 1 Summary of patient characteristics and treatment parameters

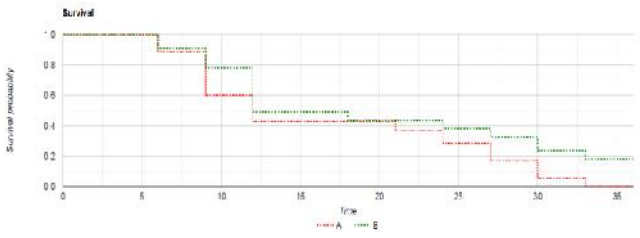
Variable	Patients who received single-fraction SRS (n35)	Patients who received multifraction SRS (n55)
Sex (female/male)	18/17	31/24
Age (y)		
Median	65	64
Range	32-78	30-80
Histology		
NSCLC	37	26
Breast carcinoma	7	11
Renal carcinoma	3	2
Other	2	2
KPS		
60-70	11	14
80-100	24	41
Extracranial disease		
Present	0	0
Absent	35	55
No. of metastases		
1	14	35
2	8	11
Size of metastases (cm)		
0.6-1.4	35	0
1.4-2	0	55

Abbreviations: KPS - Karnofsky performance status; NSCLC - non-small cell lung cancer; SRS - stereotactic radiosurgery.
* Other histologies 2 sarcoma, 1 bladder, 1 ovarian.

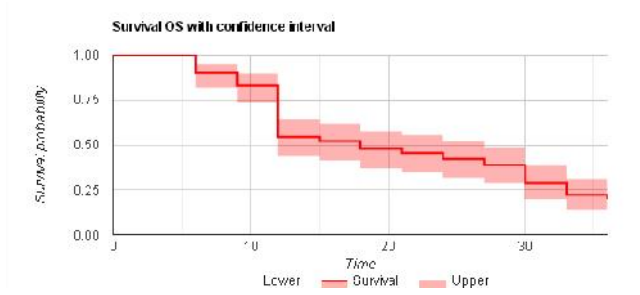
Tab 1.



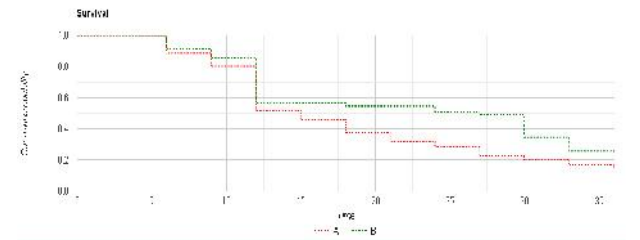
Tab 2 a



Tab 2 b



Tab 3 a



Tab 3 b

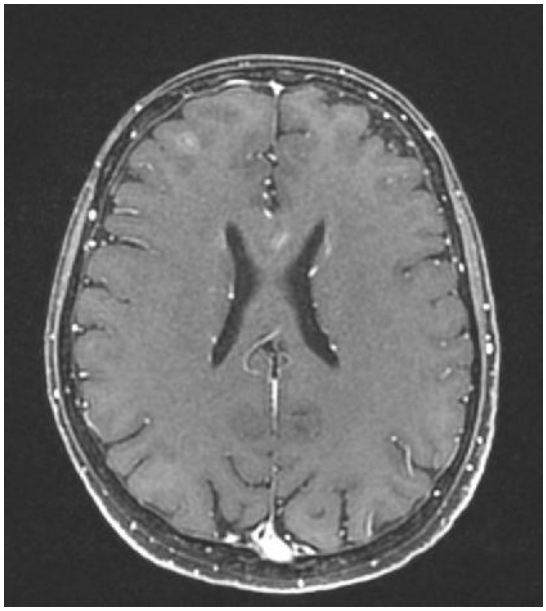


Image 1. MRI pre-RT (frontal left brain metastases)

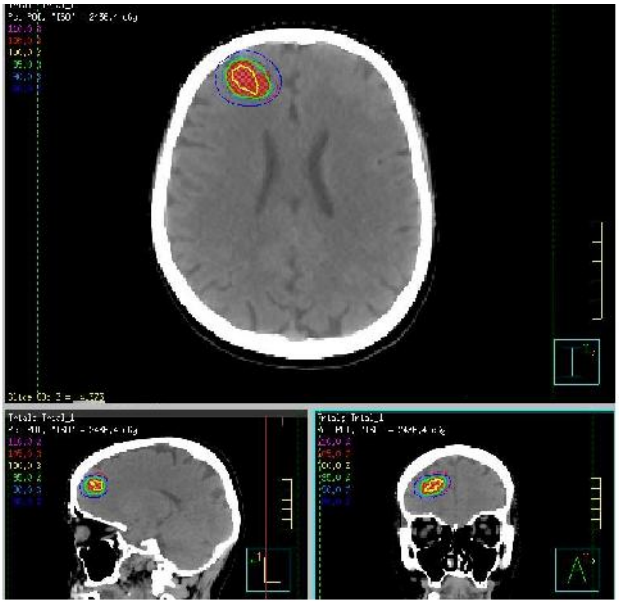


Image 2. VMAT plan (total dose 24Gy)

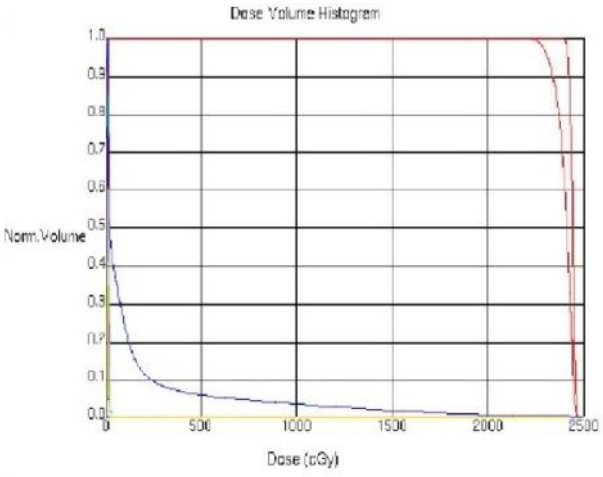


Image 3. DVH

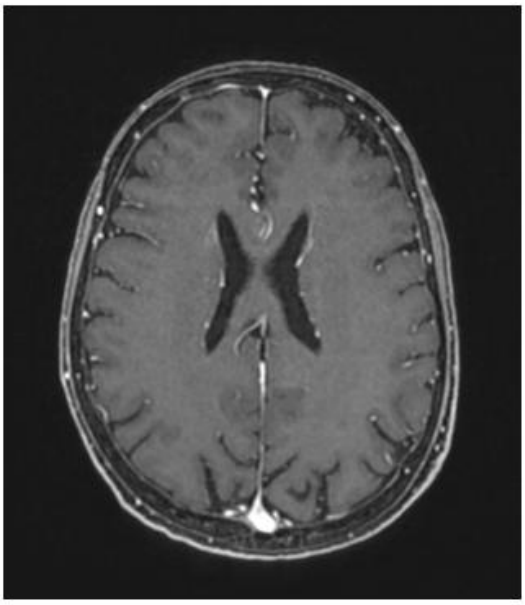


Image 4. MRI post-RT (36 months after RT)

The 1-year local control cumulative rate was 87.7 %, with 80% in the SF-SRS group (Group A) and 92.7% in the MF-SRS group (Group B).

Survivals: Survival curves were created using the Kaplan Meier method. In the univariate analysis, the log-rank test was used to compare survival curves. In all the analysis, the level of statistical significance was placed in a type I error of less than 5% ($p < 0.05$). The confidence interval (CI) was designated 95%. The 1-year PFS cumulative rate was 85.7% (42 patients) with 83.3% (15 patients) in the group A and 87% (27 patients) in the group B. Long rank test showed a statistically significant difference between the groups (p value =0.03). TAB 2 A,B. The 1-year OS cumulative rate was 54.4% (49 patients), while 51.4% (18 patients) in the group A and 56.4% (31 patients) in the group B. Long rank test showed a non statistically significant difference between the groups (p value =0.1). TAB 3 A,B

Radionecrosis: 7 patients (20%) undergoing SF-SRS and 5 (9%) subjected to MF-SRS experienced brain Radionecrosis; the 1-year incidence rate of RN was 16.6% (3 patients) and 6.4% (2 patients), respectively.

Case report: A 64 years female patient, with a single brain metastasis from SCLC was treated in June 2017, with MF-SRS (8 Gy in 3 fractions, total dose 24 Gy). The patient was put in Group B and patient's report was analyzed in our study. She had acute toxicity G1 RTOG during the treatment. She was alive at last follow up (36 months) without progression disease and a great local control without development of radionecrosis. Image 1,2,3,4

CONCLUSION

The results of this study, in which SF-SRS or MF-SRS was delivered to patients with brain metastases, indicate that both fractionation modalities showed a good survival, without statistically significant difference in term of overall survival. RN represents the most important late toxicity reported after SRS. In the present study the development of radiologic changes suggestive of RN was significantly higher in patients who received SF-SRS as compared with those receiving MF-SRS, and this was associated with an increased risk of neurologic deficits. MF-SRS at a dose of 27 Gy or 24 Gy in 3 daily fractions seems to be an effective and safety treatment modality for brain metastases, associated with better local control, progression free survival and risk of Radionecrosis. The findings address potential bias when retrospective data of two nonrandomized groups are compared. Moreover, the presence of unobserved confounding covariates may contribute to the observed differences in LC and risk of RN between groups, even when sophisticated statistical analysis are applied to reduce the impact of selection bias on outcomes. The optimal dose/fractionation radiosurgical schedules need to be determined in future studies.

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Conflict of interest: The authors declare that they have no conflict of interest.

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