Radiosurgery or Fractionated Stereotactic Radiotherapy plus Whole-brain Radioherapy in Brain Oligometastases: A Long-term Analysis

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Abstract. *Aim: To analyze the outcome of patients with brain oligometastases treated by radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) after whole-brain radiotherapy (WBRT). Patients and Methods: Overall survival (OS) and local control (LC) were evaluated in patients (patients) with 1-2 brain metastases. Results: Forty-seven patients were selected. They were submitted to WBRT (median dose=3,750 cGy) followed by SRS (17 patients; median dose=1,500 cGy) or FSRT (30 patients; median dose=2,000 cGy). Median follow-up was 102 months (range=17-151); the median survival was 22 months for the SRS group and 16 months for the FSRT group. One-year and 5-year survival was 56% and 16%, respectively, in SRT and 62.1% and 3%, respectively, in FSRT. Neither treatment proved to significantly impact OS (p=0.4). The 1-year LC rates were 80% and 61.1% in the two groups, respectively (p=0.15). Conclusion: SRS or FSRT after WBRT could offer the same outcomes in patients with brain oligometasteses. Further investigation is warranted to confirm these data and define the optimal stereotactic modality.*

Brain metastases are the most common intracranial malignant neoplasms in adults and occur in 25% to 35% of cancer patients (1). They cause significant mortality and morbidity, including cognitive impairment at the time of presentation (2). Surgery and radiotherapy are the main treatment options (3). Prognostic indicators include the number, size, location, the patient's Karnofsky performance status (KPS), age, extent of systematic disease and primary disease status (4, 5).

Patients with one or two brain metastases and with favorable prognostic features have a relatively favorable survival; thus, the treatment is frequently more aggressive than for patients with multiple brain metastases (5).

Radiosurgery (SRS) delivered as a single fraction to individual intracranial lesions has been the most common technique used to dose-escalate on lesions following whole brain radiotherapy (WBRT) and considered as safe alternative to surgical resection in small lesions (6-8). The RTOG 9502 established radiosurgery dose recommendations of 15-24 Gy for individual lesions up to 4 cm (9). However, recent clinical trials have called this practice into question due to increased neurotoxicity noted in some (10), but not all (11) studies when compared to focal therapy alone.

Fractionated stereotactic radiotherapy (FSRT) is preferred when the target is too large or located near or within critical brain structures, such as the brain stem, optic pathway or motor cortex (12, 13). Benefits of re-assortment and re-oxygenation may occur with a fractionated radiotherapy course; therefore, FSRT may be more efficacious in the treatment of brain metastases compared to single-fraction radiosurgery (12). None randomized trial has compared radiosurgery to FSRT, but published data do not seem to highlight any difference in terms of local control (LC) and overall survival (OS) (13).

A variety of alternative radiotherapeutic approaches are now available. In particular, intensity modulated arc-based conformal radiation therapy combined with image-guided radiation therapy (IGRT) system lends itself to synchronous boost strategies so multiple targets can be easily treated to different total and per fraction dose, providing a potential alternative platform to conventional stereotactic frame systems for precision radiotherapy (14).

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Recently, we implemented a volumetric arc therapy (RapidArc) and before using this novel technique to treat brain metastasis we decided to analyze a historical group of patients treated by stereotactic technique.

In this analysis, we evaluated safety and efficacy of SRS compared to FSRT after WBRT in patients with brain oligometastases.

Patients and Methods

Patients affected by brain metastases of any primary tumor and treated in our Institution with SRS or FSRT were the subject of the present study. Inclusion criteria were: no prior radiotherapy or surgery to the brain, less than 3 brain metastases, diameter ≤3 cm, confirmed by magnetic resonance imaging (MRI), controlled primary tumor, absent or controlled extracranial metastases, recursive partitioning analysis (RPA) (6-7) class 1-2.

Prior to stereotactic radiotherapy, all patients received WBRT, using a thermoplastic mask as an immobilization system; during the stereotactic phase two different systems were used: a fixed system (3D-line srl, supplier, address) for SRS and a non-invasive stereotactic relocatable immobilization system (3D-line medical system, supplier, address) for FSRT. Image fusion with MRI scan was performed to contour brain lesions in stereotactic plan. WBRT was administered by two opposite latero-lateral fields. SRS was performed by 6-megavoltage photons from a linear accelerator using multiple non-coplanar converging arcs. Until 2006, a conic collimator was used, that was replaced by a dynamic micromultileaf collimator (3D-line medical system). Treatment planning was carried out with the Eclipse Treatment Planning System (Varian, address) for the WBRT phase and with TPS Ergo (3D-line medical system) for stereotactic treatment.

The dose was prescribed to the isocenter with the 95% isodose encompassing brain for whole brain and 80 % isodose encompassing the entire gross tumor volume (GTV) for SRS. Dose-limiting structures, such as the eyes, optic nerves, optic chiasm and brainstem, were delineated according to Emami *et al.* recommendations (15).

All patients were evaluated with MRI one month after treatment and then quarterly. Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria, v 2.0.

Statistical analysis was performed by MedCalc (www.medcalc.be).

The Student's *t*-Test was used to verify the absence of statistically significant differences in the distributions of prognostic factors between the two groups.

LC rates and OS were calculated using the Kaplan-Meier method.

Cox proportional hazards regression model was used to analyze the effect of covariates on survival.

Results

We retrospectively evaluated files relative to 379 patients submitted to whole-brain radiotherapy for brain metastases from January, 1997 to March, 2010, in our Institution. Among them, 47 patients were evaluable for analysis; 25 were male and 22 female with a median age of 57 years (range=40-77). The median number of brain metastases was 1 (range=1-2). After WBRT, 17 patients were submitted to SRS and 30 patients to FSRT. The median dose of WBRT was 3,750 cGy (range=3,000-4,000) with a daily dose of 250 cGy (range=200-300). Radiosurgery was delivered with a median dose of 1,500 cGy (range=1,500-2,000), while, for FSRT, the median dose was 2,000 cGy (range=2,000-2,500) with a daily dose of 500 cGy. Using these total doses and fractionations and assuming for brain tumors an alfa/beta ratio of 10 Gy, the resulting 2Gy-equivalent dose (EQ2) was 31.25 Gy for SRS and 25 Gy for FSRT, respectively. No statistical difference was found in the two groups in terms of age, histology, number of brain metastasis and RPA class.

The patients' characteristics of the entire cohort and both treatment groups are reported in Table I.

Table I. *Patients' characteristics.*

Characteristics	Total	SRT	FSRT	*t*-Student's test (*p*-value)
No. of patients	47	17	30	NR
Age (years)	57	57	56	0.46
Primary tumor				
Lung cancer	32	14	18	
Breast cancer	10	1	9	0.19
Rectal cancer	1	0	1	
Others	4	2	2	
No of brain metastases				
1	37	16	21	0.052
2	10	1	9	
RPA Class				
1	36	12	24	0.46
2	11	5	6	
Whole brain dose (cGy/n°fr)				
3,000/10	12	3	9	
3,750/15	32	12	20	0.39
4,000/20	3	2	1	
Boost metastases dose (cGy/n°fr)				
1,500/1	14	14	0	NR
2,000/1	3	3	0	
2,000/4	21	0	21	
2,500/5	9	0	9	

The median planning target volume (PTV) was 1.82 ml for the SRS group and 2.45 ml for the FSRT group.

Toxicity. Grade >3 acute toxicities, such as headache, hearing problems, nausea and vomiting, did not occur in treated patients. With regards to chronic adverse effects, grade 3 chronic toxicities (alopecia, headache, neurocognitive and motor deficits, as well as visual/hearing impairment) occurred in 5% of the patients in SRS. Out of this group, one patient revealed radionecrosis, radiologically demonstrated and appeared 6 months after the completion of radiotherapy.

Survival. Median follow-up was 102 months (range=17-151) in all patients. The median LC was 14 months for the entire

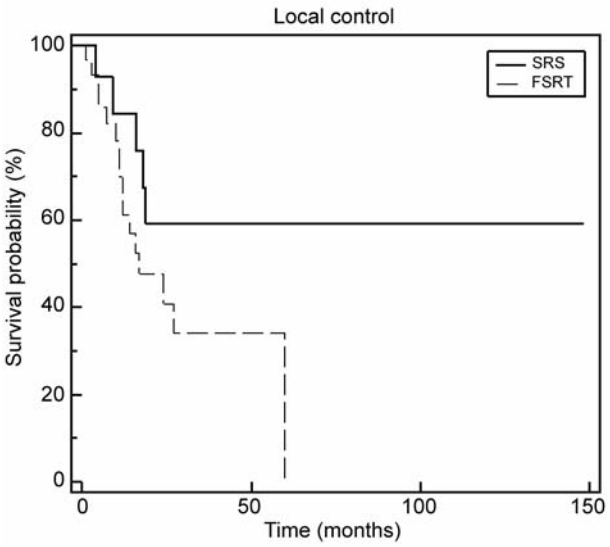

Figure 1. *Local control*.

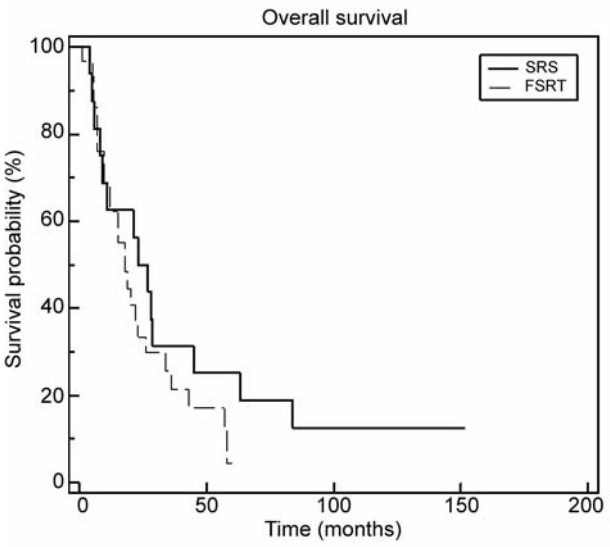

Figure 2. *Overall survival*.

cohort. No statistically significant difference was found among patients treated by SRT (18 months) with respect to those treated by FSRT (12 months) (p=0.15) (Figure 1). The 1-year LC rates were 80.0% and 61.1% in SRS and FSRT, respectively.

Median survival time was 18.5 months for the entire cohort, 22 months for patients treated with SRS and 16 months for patients treated with FSRT.

Seven patients are alive, five without disease and two with disease.

The 1- and 5-year survival were 56.0% and 16.0%, respectively, in SRS and 62.1% and 3% in FSRT, respectively. Neither treatment proved to significantly impact on OS (p=0.40) (Figure 2).

Cox proportional hazard regression showed that survival was not significantly associated with primary tumor (p=0.30), one brain metastases (p=0.60) and RPA class (p=0.57).

Discussion

Patients with brain metastases have generally a poor prognosis and WBRT is the most common treatment modality for them. Recent studies (16, 17) have demonstrated that life expectancy of these patients is influenced not only by the number of brain lesions but also by several factors, such as the presence or absence of extracranial metastases, the patient's age and Karnofsky performance score (KPS), the status of primary disease (5). Therefore, patients who have a limited number of lesions and a controlled extracranial disease could benefit from more aggressive treatments, including surgery or SRS. In fact, these therapeutic approaches represent, together with WBRT, the standard treatment of 1-3 brain metastases (18).

Radiosurgery delivered as a single fraction to individual intracranial lesions has been established as a safe alternative to surgical resection (8). We have recently published a study that compared patients who have undergone WBRT + SRS versus Surgery + WBRT (19). According to literature data (8), we observed that surgery still remains the preferable treatment in symptomatic patients but the stereotactic treatment may be an effective, non-invasive approach as alternative to surgery for patients affected by small brain metastases (<3 cm), especially when their extracranial disease is controlled and for personal or clinical reasons they are not candidates to metastasectomy. Logistically, radiosurgery requires separate localization and treatment procedures that add some inconvenience and cost for patients, providers and caregivers. Depending on the radiosurgery system used, invasive immobilization devices may be necessary, which add to patient discomfort (14). However, several studies have demonstrated a LC benefit for patients with solitary brain metastases receiving stereotactic radiosurgery in addition to WBRT, with any significant difference in overall survival only in selected groups (20-21-6). Nevertheless, it can be associated with high toxicity, especially in cases where the target is localized near or within critical brain structures, such as the brainstem, optic pathway or motor cortex. In these cases, an alternative treatment option can be the FSRT, delivering a highly conformal dose distribution in a few treatment sessions using a relocatable stereotactic frame. Futhermore, single-fraction treatments do not permit the exploitation of the potential

radiobiological benefits of re-assortment and re-oxygenation that may occur with a fractionated radiotherapy course. Hall and colleagues have suggested that fractionated regimens of stereotactic radiotherapy may provide a radiobiological advantage over SRS in the management of intracranial malignancies, even when only a few fractions are utilized (22). For malignant tumors, such as brain metastases, however, fractionated radiotherapy offers the potential to exploit the different biological responses and repair mechanisms between neoplastic and normal tissues to ionizing radiation. Brain metastases typically represent foci of acutely responding neoplastic cells immediately surrounded by late-responding healthy brain tissue.

Aoyama *et al*. (23) analyzed 87 patients treated with 35 Gy in 4 fractions. Their median survival was 8.7 months with an 81% local progression-free survival (LPFS) rate at 1 year. Toxicity developed in 4 patients (5%). The authors concluded that FSRT was as effective as SRS with less toxicity.

Narayana *et al*. (24) analyzed 20 patients not amenable to SRS because of localization or size of the tumor and who were treated with 30 Gy in 5 fractions at 2 fractions per week. The median survival was 8.5 months, with a 70% LPFS rate at 1 year. Steroid dependency, lasting over 3 months, developed in 3 patients (15%). The authors concluded that results from FSRT were comparable to those of surgery or SRS with acceptable toxicity levels.

Pizkall *et al*. (25) compared the benefits of fractionated conformal stereotactic radiotherapy with those of WBRT followed by a boost of SRS in treatment of cerebral metastases. Even thought they did not observe a statistical difference between the two groups in local tumor control, they did observe that eight patients (25%) in the group treated only with fractionated stereotactic radiotherapy developed new metastases in areas not covered by the irradiation. In contrast, none of the patients treated with WBRT and SRS boost had developed new metastases.

Recently, Kim *et al*. (13), by comparing SRS to FRST, observed that patients treated with FSRT exhibited similar survival times and LPFS rates with a lower risk of toxicity in comparison to those treated with SRS, despite the fact that FSRT was used for large lesions and lesions in adverse locations.

Unlike the majority of published reports, our study compared patients who have undergone WBRT plus SRS to patients submitted to WBRT followed by FSRT always performed by linear accelerators; this technology does not need a dedicated tool, such as the gamma-knife or cyberknife.

Our study, with the limitations of a retrospective analysis and a small simple size, proves, after a considerable follow-up, that the efficacy of FSRT is favorably comparable to SRS in terms of LC and OS, as literature data without late toxicity. As it generally occurs in this patients' population, intercurrent illness and systemic disease progression may have skewed the difference on intracranial control. Our survival analysis also failed to find any statistically significant association with the traditional prognostic factors, such as RPA class, primary tumor, number of brain lesions; these findings can be explained by selection bias, the small sample size, the effectiveness of brain metastases treatment and, also obviously, by the impact of all treatments offered to patients during their clinical history.

In order to compare the effects of various fractionated schedules used in our study, we calculated the biological equivalent dose (BED) on the linear-quadratic (LQ) model. The BED of 15 Gy in 1 fraction was 31.25 Gy10 (BED in Gy when a/b is 10) for early effects and 54 Gy3 (BED in Gy when a/b is 3) for late effects. The corresponding BED values for 20 Gy in 4 fractions were 25 Gy10 and 32 Gy3, respectively. Therefore, a similar local control with less toxicity by using FSRT was expected.

Thus, FSRT should be considered as a valid alternative to SRS for the treatment of one to three metastatic lesions and support the employment of new technology, such as intensity modulated arc-based conformal radiation therapy, to delivery simultaneous integrated boost for oligometastatic brain metastases. Further investigation is necessary to confirm these data and define the optimal dose/fractionation.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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