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A prospective phase II trial on reirradiation of brain metastases with radiosurgery

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ABSTRACT

Purpose: In our previous published trial on radiosurgery (SRS) of recurrent brain metastases (BM) after whole brain radiotherapy (WBRT), Karnofsky performance status (KPS) and administered dose conditioned outcome and late toxicity, respectively. Brain radionecrosis was registered in 6% of patients. With the aim to obtain similar satisfactory outcomes and limit toxicity, we started a phase II trial in which reirradiation of BM with SRS were done using a tighter patient selection.

Materials and methods: Patients with BM recurring after WBRT were recruited for reirradiation with SRS. Only patients with good KPS (≥70), good neurologic functional score (NFS 0-1) and lesions with a diameter ≤20 mm were considered eligible for retreatment. Dose exceeding 20 Gy was never administered.

Results: The 59 patients reirradiated had 109 BM with a diameter range of 6–20 mm. Median interval between prior WBRT and SRS was 15 months and median SRS administered dose was 18 Gy (range 10–20 Gy). Complete and partial response (CR, PR) was obtained in 42% of patients with 2 years of control rate of 81%. Median overall survival (OS) after reirradiation was 14 months. No radionecrosis was detected.

Conclusions: Analysis of our current trial compared with results of our previous data suggests that a tighter patient selection (KPS ≥ 70; NFS 0-1, BM with ≤20 mm of diameter) and SRS dose ≤20 Gy allowed a high OS rate, a good percentage of CR and PR which last for >2 years, and no brain radionecrosis.

1. Introduction

With advances in imaging and in therapeutic options and a corresponding improvement in survival, brain metastases (BM) are now diagnosed more frequently than in the past. Whole brain radiotherapy (WBRT) was long considered to be the standard treatment for patients with extensive intracranial disease. Often recurrence continues to occur in the brain after WBRT and require further therapeutic intervention [1–4]. Reirradiation with WBRT is generally few used because of its potential neurotoxicity [5–8]. Stereotactic radiosurgery (SRS) appears to be a proper approach considering its high precision in delivering dose to the affected tumor limiting the irradiation of surrounding brain tissues already treated with WBRT. Although much has been written about prognostic factors in patients with newly diagnosed BM [9–11], there is few sure information about BM patient selection for reirradiation [2,3,12].

In this clinical setting, a good Karnofsky performance status (KPS), absence of debilitating neurologic deficits and/or mass effect, 1–4 BM, primary controlled and/or indolent disease, and previous WBRT done at least 4–6 months before reirradiation are the most important variables used in clinical practice [1,8,11,12]. As well, administered doses are generally those suggested by the Radiation Therapy Oncology Group (RTOG) protocol 90–05 on the maximum tolerated dose of SRS after WBRT [13].

In our previous retrospective trial, SRS as salvage treatment of recurrent BM after WBRT resulted feasible and effective. Administered dose and patient selection conditioned outcome and late toxicity. Particularly, SRS dose ≥23 Gy and response after SRS (complete and partial response better than stable disease) were

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significantly associated to a longer duration of response. Karnofsky performance status (KPS) and neurologic functional status (NFS) resulted the two variables that significantly affected a better overall survival (OS). A suboptimal result of this trial was the appearance of brain radionecrosis in patients having a lesion diameter of more than 20 mm or in those reirradiated with doses of 23 Gy or more. So, good KPS, good NFS and tumour diameters inferior to 20 mm were the prognostic factors which positively conditioned outcome of our patients, while doses higher than 23 Gy, though associated to a long duration of response, were also a possible cause of radionecrosis [12].

Starting from these findings, we decided to continue the reirradiation with SRS of recurrent BM after WBRT in a prospective phase II trial using a tighter patient selection and doses $\leq$20 Gy. Results of this trial are reported.

2. Materials and methods

2.1. Study endpoints

The objective of this mono-institutional prospective phase II trial was to verify if a tighter patient selection and doses $\leq$20 Gy in the reirradiation with SRS of recurrent BM after WBRT ensure satisfactory results in terms of response, duration of response and survival limiting at the same time incidence of brain radionecrosis. Outcomes of this trial were compared with those obtained in our previous retrospective trial.

2.2. Eligibility criteria

Patients with BM diagnosed at gadolinium magnetic resonance imaging (MRI) that recurred after WBRT were considered for reirradiation with SRS. All cases were preliminarily discussed in a multidisciplinary meeting with radiation oncologists, neurosurgeons, neuroradiologists, medical oncologists, and pathologists to define the clinical indications. Eligible patients were those with a KPS of $\geq$70, NFS of 0-1 (score 0, no neurologic symptoms; score 1, minor neurologic symptoms), 1–4 lesions with a diameter of $\leq$20 mm, primary controlled and/or an indolent progressive disease, and a previous WBRT carried out at least 6 months before reirradiation. Patients who did not enter in the protocol were submitted to surgery in presence of mass effect, to fractionated stereotactic radiotherapy (FSRT) when BM diameter was more than 20 mm and/or embedded into critical cerebral structures, or to only supportive care because of bad general condition and life expectancy of 3 months or less.

2.3. Treatment and follow up

A linear-accelerator-based SRS was done and treatment procedures as well steroid administration was already described elsewhere [12]. The dose prescription was generally between 18 and 20 Gy. Only in case of BM strictly located near critical cerebral structures lower doses were prescribed. Our referent ethical committee approved this trial and informed consent was obtained according to the rules of our Institution.

Patients were followed performing MRI and clinical examination 3 months after SRS, and at 3-month intervals thereafter. In addition, the single-photon emission computed tomography (SPECT-CT) examinations were scheduled when there was a need to differentiate between radiation-induced necrosis or tumor progression [14].

2.4. Assessment

As we did in the previous retrospective trial, response to treatment was evaluated according to MRI imaging. Complete response (CR), was defined as complete resolution of the enhancing lesion, partial response (PR), >50% reduction in the size of the lesions, stable disease (SD), no change in the dimension of the lesion, or <50% reduction, and progression disease (PD), >25% increase in the size of the lesion. Local control was achieved if there was a lack of progression of the irradiated BM and brain control was defined as local control in absence of other documented BM. Duration of local control was assessed separately for each lesion and was measured from the date of SRS until MRI documentation of failure at the treated site. Lesions in patients who died with no evidence of relapse were considered censored at the time of death for this end point. A brain failure at the site of SRS was defined in-field relapse, whereas the appearance of new BM was defined out-field relapse.

To study which factors were prognostic for duration of response and survival, lesions and patients were stratified by histology of primary disease, status of extra cranial disease, dimension and number of BM at the time of SRS, prescribed doses, response after SRS (CR and PR versus SD), interval between prior WBRT and SRS. Survival was also calculated according to sex, age, KPS, and NFS [12].

Acute and late toxicity were assessed according to the Radiation Therapy Oncology Group-RTOG Morbidity Scoring Criteria [15]. Radionecrosis was suspected when MRI showed local changes in the lesion, with irregular enhancement, associated with surrounding edema without mass effect. In this case, SPECT-CT was performed with a semi-quantitative analysis to obtain the Technetium-99m 2-methoxyisobutylisonitrile (^{99}mTc-MIBI) uptake index. Diagnosis of brain radionecrosis was done when ^{99}mTc-MIBI uptake resulted $\leq$2 [12,14].

2.5. Statistical methods

Duration of response and survival probability were estimated with the Kaplan–Meier method. Log-rank test was used to test whether there was a difference between the survival times of different group of patients and treatment factors. Variables that showed significant values were further re-entered for multivariate Cox proportional hazard regression model to analyze the hazard ratio (HR) of the potential prognostic indexes for these outcomes [16]. A value of $P < 0.05$ (two tailed) was considered statistically significant. Data were analyzed using a statistical software package (MedCalc 11.1 Broekstraat 52, B-9030 Mariakerke Belgium).

3. Results

Between December 2008 and December 2016, 64 patients with 118 BM were recruited for reirradiation with SRS. Five (8%) patients with 9 (8%) BM was lost to follow-up, so patients and BM evaluable for all clinical outcomes were 59 and 109, respectively. At time of analysis, all but 3 patients had died. Distribution of evaluable patients according to KPS, NFS, primary tumour histology and status of extra cranial disease was shown in Table 1. Median age was 62 years (range 40–82). All patients had a KPS $\geq$ 70% and a NFS $\leq$ 1 with only 24% of patients with minor neurologic symptoms. Lung and breast cancers were the most represented primary tumours (20% and 18%, respectively). Primary tumours were controlled in 77% of cases. The median interval between prior WBRT and SRS was 15 months ranging from 6 to 169 months.

Table 1
Distribution of the 59 eligible patients according to KPS, NFS, primary tumor histology and status of extracranial disease.

Variables	Number of patients	%
Sex		
M	21	36
F	38	64
KPS		
100	32	54
90	21	36
80	4	7
70	2	3
NFS		
0	45	76
1	14	24
Primary tumor histology		
Breast	20	34
Non-small cell lung cancer	18	31
Small cell lung cancer	9	16
Melanoma	3	5
Colorectal	2	3
Ovarian	2	3
Kidney	2	3
Others	3	5
Status of extracranial disease		
controlled primary tumor	46	77
local or indolent progressive disease	13	23

Legends: KPS, Karnofsky performance status; NFS, neurologic functional status.

The WBRT doses were 30 Gy in 10 fractions in 43 (73%) patients and 20 Gy in 5 fractions in 16 (27%) patients. The median number of treated BM per patient was 2 (range, 1–4). SRS was performed in 29 (49%) patients for one BM, in 17 (29%) for 2, in 8 (14%) for 3, and in 5 (8%) for 4 BM. Lesions located in the supratentorial and posterior lobes were 60 (60%) and 39 (40%), respectively. The median lesion diameter and lesion volume were 10 mm (range, 6–20) and 0.6 cc (range, 0.1–4.2 cc), respectively. Maximum diameter of treated BM resulted $\leq$10 mm, 11–19 mm, and 20 mm in 48 (48%), 39 (40%) and 12 (12%) lesions, respectively. Median administered SRS dose was 18 Gy (range, 10–20), fifty-nine (60%) BM received $\geq$18 Gy.

Cause of death was brain failure in 18 (31%) patients, systemic progression in 28 (47%) patients, of these 17 had a brain control and 11 a brain failure. The majority of patients with systemic progression, were treated with different chemotherapy schedules chosen according to primary tumor histology. Ten (17%) patients died for causes not correlated to the cancer. Three (5%) patients are alive.

Brain failure was registered in 30 (51%) patients, 15 (25%) had out-field relapse, 7 (12%) in-field relapse, and 8 (14%) in- and out-field relapse. Of 15 patients with out-field relapse, 4 were treated with SRS, 6 with chemotherapy, and 5 were followed with no further treatment. Of 7 patients with in-field relapse, 1 was retreated with SRS, 4 underwent resection with pathology confirming recurrent disease, 2 received chemotherapy, and 1 was submitted to only supportive therapy. Of 8 patients with in- and out-field relapse, 4 were treated with chemotherapy and 4 no further treatment.

Three months after reirradiation, 99 (91%) BM responded to reirradiation (14, 14% CR; 28, 28% PR; 57, 58% SD) and 10 (9%) lesions progressed. Duration of response was 81% ± 4.5% at 1 and 2 years and 64% ± 8% at 3 years and it was associated to lesion diameter ($\leq$1 cm better than >1 cm) and to response achieved after SRS (CR and PR better than SD). Lesion diameter resulted statistically significant both at univariate and multivariate analysis, while response achieved after SRS was significant only at univariate analysis and with a trend of significance to multivariate analysis (Table 2). Other examined variables did not affect duration of response.

Median follow-up was 14 months (range, 1–107). Median OS from diagnosis of first BM was 30 months (range, 6–177). After reirradiation, median OS was 14 months (range, 1–107), and survival probability at 1, 2, and 3 years was 57% ± 6, 18% ± 5, 13% ± 4, respectively (Fig. 1). No one of the examined variables significantly conditioned OS.

Treatment was well tolerated and no more than grade (G) 2 acute toxicities were observed. Headaches and nausea/vomiting were registered in 5 (8%) patients in which the brain MRI given to better define clinical scenario showed peritumoral oedema. A medium dose of steroids (i.e., 8 mg × 2/*d* of dexamethasone) was prescribed, symptoms regressed in 3–7 days, and the MRI done after 3 months evidenced a disappearing of peritumoral oedema.

No radionecrosis was observed after the first reirradiation with SRS. A G2 brain radionecrosis (i.e., moderate neurological symptoms, corticosteroids indicated) was registered in a patient already submitted to WBRT and then twice reirradiated with SRS in the same area. She was a 61-year-old female in good clinical condition (100% of KPS) affected by non-small cell lung cancer with BM. Thirteen months after WBRT (20 Gy in 5 fractions of 4 Gy), she

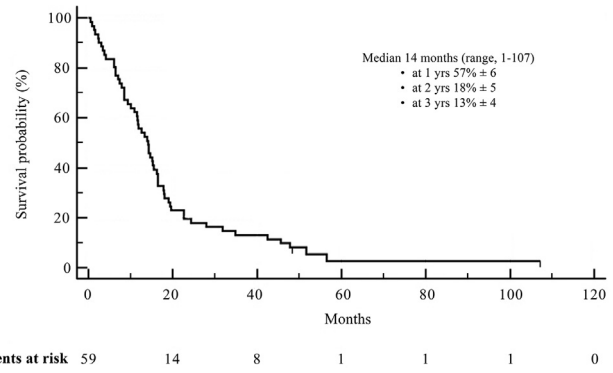

Fig. 1. Overall survival probability from reirradiation with radiosurgery (median survival 14 months).

Table 2
Variables which significantly affected 1-year local control rate at univariate and multivariate analyses.

Variables	Univariate analysis		Multivariate analysis		
	1 year ± SE (%)	*P* value	Hazards Ratio (95% CI)	*P* value	Better prognosis association
Lesion diameter					
$\leq$1 cm	87 ± 5	0.02	2.58 (1.01–6.75)	0.05	Lower diameter
>1 cm	74 ± 7				
Response					
CR and PR	93 ± 4	0.03	2.62 (0.94–7.34)	0.06	CR and PR
SD	71 ± 7				

Legends: CI, confidence interval; SE standard error; SD, stable disease; CR, complete response; PR, partial response.

underwent a first reirradiation with SRS at a dose of 16 Gy for a single left frontal lesion of 20 mm of diameter. Thirty-nine months later, she was submitted to other 14 Gy for a second SRS for an in-field relapse measuring 4 mm in diameter. Cumulative biological effective dose ($BED_{cumulative}$) was 316 Gy_2 (i.e., 60, 144 and 112 Gy_2 for WBRT, first SRS and second SRS, respectively). Diagnosis of radionecrosis was confirmed by a MRI spectroscopy which evidenced a low peak of choline, and ^{99}mTc-MIBI SPECT-CT in which the lesion had a MIBI index <2. Moderate dose of corticosteroids was prescribed and clinical symptoms regressed within 1 month. Three months after diagnosis of radionecrosis, MRI assessed a reduction of oedema. At follow-up, patient is still alive with brain control of disease.

The $BED_{cumulative}$ in our patients never exceeded RTOG 90–05 protocol recommendations [13] ($\leq$387 Gy_2 for lesions diameters $\leq$20 mm), so that median $BED_{cumulative}$ was 240 Gy_2 (range, 135–295), also in twice reirradiated patient.

No other late toxicities or new permanent neurologic deficits were observed in reirradiated patients.

Three months after reirradiation changes in KPS and NFS were analyzed. Of 32 patients with KPS 100, 30 (94%) maintained their score and 2 (6%) worsened from 100 to 80. Of 21 patients with KPS 90, 3 (14%) improved to 100, 17 (81%) maintained their score, and only 1 (5%) worsened from 90 to 70. Of 6 patients with KPS (i.e., 80 and 70), only 1 (17%) improved from 80 to 90. Of 45 patients with NFS 0, 28 (62%) maintained their score and 17 (38%) worsened (14 from 0 to 1, and 3 from 0 to 2). Of 14 patients with NFS 1, 9 (65%) improved from 1 to 0, 3 (21%) maintained their score and 2 (14%) worsened from 1 to 2. If patients who improved or maintained their KPS and NFS are considered responders, total response rate were 87% and 68%, respectively. Of note, no patient reached KPS inferior to 70 and only 5 (8%) patients worsened from NSF 0-1 to NFS 2 (score 2, moderate neurologic symptoms).

4. Discussion

Due to the improved therapeutic and diagnostic approaches, and longer patient survival, BM are an increasingly common problem. In addition to chemotherapy, possible treatment options are surgery and/or SRS when the number of BM is limited to 1– 4, while the standard therapy for patients with multiple BM is still WBRT [17,18].

Recently, a prospective observational study has shown that SRS in patients with 5–10 BM is non-inferior to that in patients with 2–4 BM [19]. Results has been confirmed at 2-year additional follow up [20]. Other trials have been published regarding the possibility to treat simultaneously multiple BM comparing a single isocentre technique versus a multi-isocentre approach. The two techniques resulted similar in outcome but the first one had the advantage of giving the treatment in fewer time with lower health brain irradiation [21,22]. The rationale of this extensive use of SRS derives from the possible WBRT-associated neurocognitive toxicity and the availability of last generation linear accelerators able to administer SRS in few time on multiple BM [19]. Apart from this novel approach which should be still validated, in clinical practice WBRT remains the standard treatment for patients with extensive intracranial disease [17,18].

After WBRT there are a certain number of long survival patients who recur in the brain and require further therapeutic intervention [1–4]. Re-irradiation with WBRT is generally few used considering the possible associated neurotoxicity [5–8]. Aktan et al. and Sharp et al. have recently published two interesting retrospective studies in which reirradiation of multiple BM with low-dose WBRT (20–25 Gy in 10 fractions) after a prior WBRT resulted beneficial and associated to a minimal toxicity in select patients with good **KPS** and without severe symptoms [4,23].

Anyway, for patients with a small number of metastases recurring after WBRT, SRS is the preferred option while surgery is reserved to patients with neurologic symptoms related to mass effect or in case of diagnostic doubts [4,8,12,13]. Considering that only a certain number of patients can benefit from an active retreatment with SRS, it is necessary an appropriate patient selection. Generally, selection is based on good KPS, absence of debilitating neurologic deficits, 1–4 BM, primary controlled and/or indolent disease, and previous WBRT carried out at least 4–6 months before reirradiation [1,2,8,24,25]. These selection criteria should be adopted not only when reirradiation of BM was done with no dedicated linear accelerators but also with dedicated machines as GammaKnife or CyberKnife [26]. Another important criterion to adopt in the reirradiation of BM with SRS is the compliance to the dose constrains suggested by RTOG 90–05 protocol in which dose prescription was chosen according to maximum diameter of the tumor, that is 24 Gy, 18 Gy, and 15 Gy for tumors $\leq$20 mm, 21–30 mm, and 31–40 mm, respectively [13]. These selection criteria and dose prescriptions were used also in our already published retrospective trial [12] with results similar to the best reported in literature [3,4,8,13]. Response was obtained in 91% of lesions with 1-year local control rate of 74 ± 4%. Median overall survival after reirradiation was 10 months. A suboptimal result of this trial was the appearance of SRS-induced brain radionecrosis in 4 (6%) patients. Administered dose and patient selection conditioned outcome and late toxicity. Particularly, SRS dose $\geq$23 Gy and response after SRS (CR and PR better than SD) were significantly associated to a longer duration of response. Good KPS and NFS resulted the two variables that significantly affected a better OS. Brain radionecrosis was registered in 2 patients with a lesion diameter of more than 20 mm and in the others 2 administered doses were 23 Gy or more. So, good KPS, good NFS and tumour diameters inferior to 20 mm were the prognostic factors which positively conditioned outcome of our patients, while doses higher than 23 Gy, though associated to a long duration of response, were also a possible cause of radionecrosis [12].

Starting from these findings, we decided to continue the reirradiation with SRS of recurrent BM after WBRT in a prospective phase II trial eliminating all variables which had negatively conditioned prognosis, that are KPS of $\leq$70, NFS of >1, lesion diameter of >20 mm and prescription of doses >20 Gy. So, we have adopted a tighter patient selection enrolling only those with KPS of $\geq$70, NFS of 0-1, 1–4 lesions with a diameter of $\leq$20 mm, and dose prescription was of $\leq$20 Gy. The other selection criteria already used and turned out adequate were as well adopted (i.e., a primary controlled and/or an indolent progressive disease, and a previous WBRT carried out at least 6 months before reirradiation). With this changes, duration of response was associated to lesion diameter ($\leq$1 cm better than >1 cm) and to response achieved after SRS (CR and PR better than SD), while no examined variables influenced survival.

There are several considerations to do comparing the current prospective trial with our previous retrospective one. Although, in both trials more than 70% of patients had controlled extracranial disease, in the current trial patients with better KPS ($\geq$70%) and higher NFS ($\leq$1) are more represented (100% vs 75% and 100% vs 75%, respectively). Median interval between WBRT and SRS was longer in the current trial than in the previous one (15 vs 11 months, respectively). In the current trial range of lesion diameters and lesion volumes were 6–20 mm and 0.1–4.2 cc, respectively; all these values were largely lesser than in the previous trial (5–35 mm and 0.1–23 cc, respectively). Administered doses never exceeded 20 Gy (median 18 Gy, range, 10–20), whereas in the previous trial doses were higher (median 20 Gy, range, 12–25), but total lesion response (i.e., CR, PR, and SD) was the same

Table 3
Comparison of patient outcome between previous and current trial.

Trials	N. of evaluable patients/ lesions	Patients with KPS > 70	Patients with controlled extracranial disease	Median interval between WBRT and SRS (range)	Median lesion diameter/volume (range)	Median administered SRS dose (range)	Total lesion response*	Duration of response at1 and 2 years	N. of patients with brain radionecrosis
Previous	69/137	75%	72%	11 months (2–84)	12 mm/1 cc (5–35 mm/0.1–23 cc)	20 Gy (12–25 Gy)	91%	74% and 69%	4 (6%)
Current	59/109	100%	77%	15 months (6–169)	9 mm/0.6 cc (6–20 mm/0.1–4.2 cc)	18 Gy (10–20 Gy)	91%	81% and 81%	0

Legends: KPS, Karnofsky performance status; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery.
* Complete response, partial response, and stable disease.

(91%) in both trials, and duration of response at 1 and 2 years resulted fairly higher in the current with respect to previous trial (81% and 81% vs 74% and 69%, respectively). Apart from a patient twice reirradiated, no brain radionecrosis was documented in the current trial. Median overall survival probability from reirradiation was 14 months in the current versus 10 months in the previous trial (Table 3).

In conclusion, this phase II trial on reirradiation of BM with SRS showed that a tight patient selection on the basis of good KPS and NFS, lesion diameter not exceeding 20 mm, and prescribed SRS doses of 20 Gy or less allowed a good percentage of long lasting response, a high OS rate, and acceptable acute toxicity without iatrogenic brain radionecrosis. Considering that on this topic there are neither phase III randomized trials nor prospective ones, our report can be useful in clinical practice for the selection of patients who are like to benefit and the prescription of adequate dose in the reirradiation of BM with SRS.

Compliance with ethical standards

This study was not funded.

Conflict of interest

None declared.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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