Original Article

Adaptive hypofractionated gamma knife radiosurgery in the acute management of brainstem metastases

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Abstract

Background: Intrinsic brainstem metastases are life-threatening neoplasms requiring rapid, effective intervention. Microsurgery is considered not feasible in most cases and systemic treatment seldom provides a successful outcome. In this context, radiation therapy remains the best option but adverse radiation effects (ARE) remain a major concern. A dose-adaptive gamma knife procedure coined as Rapid Rescue Radiosurgery (3R) offers the possibility to treat these lesions whilst reducing the risk of ARE evolvement. We report the results of 3R applied to a group of patients with brainstem metastases.

Methods: Eight patients with nine brainstem metastases, having undergone three separate, dose-adapted gamma knife radiosurgery (GKRS) procedures over 7 days, were retrospectively analyzed in terms of tumor volume reduction, local control rates, and ARE-development under the period of treatment and at least 6 months after treatment completion.

Results: Mean peripheral doses at GKRS 1, GKRS 2, and GKRS 3 were 7.4, 7.7, and 8.2 Gy (range 6–9 Gy) set at the 35–50% isodose lines. Mean tumor volume reduction between GKRS 1 and GKRS 3 was –15% and –56% at first follow-up. Four patients developed radiologic signs of ARE but remained clinically asymptomatic. One patient developed a local recurrence at 34 months. Mean survival from GKRS 1 was 13 months. Two patients were still alive at the time of paper submission (10 and 23 months from GKRS 1).

Conclusions: In this study, 3R proved effective in terms of tumor volume reduction, rescue/preservation of neurological function, and limited ARE evolvement.

Key Words: Adaptive hypofractionated radiosurgery, adverse radiation effects, brainstem metastases, gamma knife, recursive partitioning analysis

INTRODUCTION

The brainstem is delicately structured in a network of highly functional, well-organized distinct centers with unique neuro-physiological functions crucial for survival. Although only accounting for about 5% of all intracranial metastases,[39] intraparenchymal brainstem metastases require prompt, effective treatment to avoid severe neurological impairment and ultimately death. However, there is no general consensus for optimal management of these lesions, particularly in cases with local in field recurrences after radiation therapy. Microsurgery is often considered not suitable due to the complex anatomy and the potential for profound iatrogenic neurological deficits. With the exception of high-dose methotrexate (such as in cases of systemic lymphoma), most chemotherapy remains inefficient due to the constraints imposed by the blood–brain barrier.[23,84] Despite substantial advances in the field of immunotherapy, the overall/long-term therapeutic effects on brain metastases remain limited for most patients with different tumor histologies.[9] Due to the latter reasons, radiation therapy is often considered as the treatment of choice. In this context, whole-brain radiation therapy (WBRT) is often contemplated, particularly in the presence of coexisting lesions other than those located in the brainstem. Yet, the efficiency of WBRT may be limited in the face of radioresistant neoplasms such as melanoma or renal cell cancer and is intrinsically associated with the development of neurological side effects.[14,21,47,51,65] WBRT is therefore increasingly postponed if the patient has significant remaining life expectancy from a systemic perspective.

For such cases, single fraction radiosurgery has emerged as a valid treatment alternative in the management of small metastatic brainstem lesions.[6,28,35,39,50,79,86,89] However, due to the risk of adverse radiation effects (ARE), single fraction radiosurgery may not be suitable in the setting of brainstem metastases larger than 1 cm^3,[42,44,76] particularly in cases with significant perilesional edema and in the framework of previous radiotherapy to the region of interest. Several authors have described effective treatment via stereotactic hypofractionation for large brain metastases in terms of local control and a limited risk of ARE.[15,19,29,34,40,73,76,78,90] Through a previous publication, our group reported the effects of adaptive hypofractionated gamma knife radiosurgery (GKRS) in the management of a large brainstem metastasis;[76] the systematic application of this procedure in distinct acute/subacute settings has been coined Rapid Rescue Radiosurgery (3R).[76,78] Since the initial report, we have treated seven further patients with metastatic brainstem lesions. The objective of this retrospective analysis is to study the short- and long-term effects of such 3R treatment in the management of brainstem metastases in a total of eight patients with a focus on local tumor control, ARE development, and preservation of neurological function.

MATERIALS AND METHODS

For this study, a total of eight patients with nine intrinsic brainstem lesions were analyzed after treatment with 3R at our Gamma Knife unit (Department of Neurosurgery, Karolinska University Hospital, Stockholm) between November 2013 and October 2016. Patient characteristics are summarized in Table 1. A retrospective analysis of all medical records, treatment and follow-up imaging, and LGP (Leksell Gamma Plan) volume data was performed in all patients with institutional and ethic committee approval. This retrospective study included patients having completed 3R treatment (GKRS 1–3) with at least one follow-up MRI. The inclusion criteria for 3R treatments were as followed:

1. Patients who were not suitable candidates for microsurgical removal, other forms of radiotherapy, or systemic treatment targeting the intracranial lesion at hand (multidisciplinary selection)
2. Patients who were not suitable candidates for single fraction GKRS due to following constraints: $V_{10Gy} > 1$ cm^3 (outside the tumor bed) when applying a peripheral prescription dose of 16–18 Gy with prior radiotherapeutic focal impact on the brainstem (such as WBRT) or $V_{10Gy} > 3$ cm^3 when applying a peripheral prescription dose of 16–18 Gy without previous radiotherapy
3. Karnofsky performance status (KPS) at least 70 and Recursive partinioning analysis (RPA) of 1-2 when possible. However, exceptions were considered (KPS <70, RPA 3) in cases of compression of the fourth ventricle requiring acute salvage of neurological function and/or avoidance of imminent neurological death ("compassionate" treatment)
4. Presence of compression of the fourth ventricle and/or perilesional edema was not a hindrance for treatment (regardless of extension). Although absent in all cases, radiological evidence of evolving hydrocephalus was not a contraindication, particularly if cerebrospinal fluid (CSF)-diversion procedures were deemed not possible/indicated.

The 3R-treatment plan consisted of three separate GKRS sessions scheduled/delivered every 60–72 h over a period of 7 days. The Leksell Coordinate Frame G (Elekta AB, Stockholm) was mounted utilizing local anesthesia prior to each session, which included a stereotactic MRI and subsequent GKRS. No margins were added to the gross tumor volume (GTV) due to the rigid skeletal fixation of the G-frame (GTV = PTV [planning target volume]). Planning MRI was performed on a 1.5-T GE Discovery 450 MR (General Electric) with the fiducial box attached to the mounted frame. The stereotactic MRI examination

Table 1: Patient characteristics at the time of 3R treatment (GKRS 1-GKRS3). *Lower 10 Gy-coverage due to prior WBRT (patient 4) and local anatomo-topographical constraints (patient 6)

Patient	Diagnosis	Age	KPS/RPA at GKRS 1	Cortisone at GKRS 1	Tum. vol. (cm³) GKRS 1-3	Prescription dose (Gy), GKRS 1-3	10 Gy cov. (%) at GKRS 1-3	Brainstem location
1	Melanoma	54	100/2	Yes	1.4/1.0/1.1	8.0/8.0/8.5	78/79/86	Midbrain (central)
2	Breast cancer	74	80/2	Yes	2.9/2.7/2.5	8.0/8.5/9.0	82/83/94	Pons
3	Lung adenocarcinoma	71	90/2	Yes	1.8/1.6/1.5	8.0/8.5/8.5	86/92/92	Pons
4	Lung adenocarcinoma	41	90/2	Yes	9.2/9.3/7.6	6.0/6.0/7.0	43/47/64*	Pons
5	Breast cancer	51	80/2	Yes	0.3/0.2/0.2	7.0/8.0/8.0	48/77/74	Midbrain (sup colliculus)
					0.5/0.4/0.3	7.0/8.0/8.5	49/68/83	Midbrain (inferior colliculus)
6	Ovarian cancer	61	70/3	Yes	4.8/5.1/5.1	7.0/7.0/8.0	59/69/78*	Pons/Medulla oblongata
7	Lung adenocarcinoma	78	70/2	Yes	7.1/8/7.6	8.0/8.0/8.0	75/78/75	Pons
8	Breast cancer	64	90/2	Yes	5.2/5.1/5	7.5/7.5/8.5	69/70/83	Pons

for each session included sagittal T1 spin echo sequences at a slice thickness of 4 mm as well as a 4 mm axial T2-weighted propeller sequence to assess the extent of perilesional edema. For GTV delineation, we used post-gadolinium (0.4 ml/kg of dotarem 279.3 mg/ml, range 20–35 ml) contrast-enhanced axial T1-weighted fast spin echo sequences supplemented by 3D T1-weighted FSPGR MR. All images were reviewed in detail by experienced neuroradiologists and gamma knife surgeons prior to the planning phase (LGP treatment planning system, version 10.1.1, Elekta instruments AB, Stockholm).

In this small series of eight individual patients, there were two men and six women aged 41–78 years (mean 61.8 years). The primary tumor pathology had been identified as lung adenocarcinoma in three cases, breast cancer in three cases, and malignant melanoma and ovarian cancer in the remaining two subjects, respectively [see Table 1]. Five patients had ongoing systemic treatment at the time of 3R. Two patients had undergone WBRT prior to their 3R (patients 4 and 5); all patients received cortisone treatment for their lesions. One patient was treated for two synchronous lesions in the brainstem (patient 5). The Karnofsky score for all patients at the time of GKRS 1 was 70 or higher, and seven patients were categorized as RPA class 2 [Table 1].

Prescription doses at GKRS 1 were set upon the following variables: (1) dose-volume estimates required to achieve ablation (including potential V_{10Gy}-associated responses, see "Discussion" section) whilst minimizing the risk of ARE-development, (2) regional factors such as the presence of edema and the degree of subregional functionality/sensitivity, (3) added biological dose estimates from previous focal or adjacent radiation in terms of past dose distributions to the intended target and surrounding healthy tissues (with or without previous ARE), (4) optimal assessment of overall metastatic disease in- and outside the central nervous system, (5) concurrent clinical status at the time of treatment (KPS/RPA), and (6) the identification of histology surrogate predictors of "natural" response to radiation ("radiosensitive"

vs. "radioresistant" tumors) including a concise analysis on past responses to extra- and intracranial therapies.[1,6,8,28,31,32,36,39,43,48,51,57,67,76,78,85,89] Prescription doses at GKRS 2 and 3 were set upon the above variables and tumor volume dynamics during treatment.[76,78] With respect to variable (1), intratumoral (ablative) dose-volume thresholds for 3R-treatment planning (at each GKRS) were set at V_{10Gy} >70% (when possible).

In this regard, the mean dose prescribed for the respective treatment session (termed GKRS 1–3) was 7.4, 7.7, and 8.2 Gy, respectively. The lowest mean prescription dose was 6.0 Gy and the highest dose employed was 9.0 Gy. The prescription isodose varied from 35% to 50%. Technical treatment details are summarized in Table 1.

RESULTS

Mean overall survival time for the entire cohort from GKRS 1 to last follow-up MRI was 13 months (range: 1 month–38 months, see Table 2). Amongst the patients included here, six out of our total of eight survived at least 6 months after GKRS 1; in this subgroup ($n = 6$), long-lasting tumor control until last follow-up was achieved in five patients [Table 2]. The remaining patient (patient 1) developed a recurrence in the field of treatment at 34 month follow-up; the corresponding sequential MR- and PET-imaging post-3R demonstrated a residual component not having fully responded to treatment [Figure 1]. This is possibly due to the radioresistant nature of the underlying histology (melanoma) and insufficient 10-Gy-coverage [see Table 1]. Despite these adverse circumstances, the patient survived 38 months after GKRS 1; he died of both intra- and extracranial disease progression. Overall, two patients were still alive at the time submission of this manuscript. Of note, all other patients succumbed due to their extracranial disease. The lowest prescription dose was prescribed in patient 4 due to previous WBRT and given an underlying radiosensitive pathology (lung adenocarcinoma). In the subgroup of

Table 2: Treatment outcome in terms of tumor volume dynamics, development of ARE, KPS/RPA, and survival from GKRS 1

Patient	GKRS-induced ARE	Tumor vol. at first follow-up MRI (cm³)	KPS/RPA at first follow-up MRI'	Tumor vol. at last follow-up MRI (cm³)	Time of survival from GKRS 1
1	No	0.9	90/1	4.67**	38 mo.
2	Yes	0.4	80/2	0.484	16 mo.
3	No	1.0	60/3	1.00	2 mo.
4	Yes	3.1	100/1	5.34***	15 mo.
5	Yes	0.1	80/2	0.043	10 mo.*
		0.1		0.09	
6	Yes	2.2	80/2	0.995	8 mo.
7	-	3.4	40/3	3.39	1 mo.
8	No	3.5	100/2	0.038	23 mo.*

*Patients still alive at the time of paper submission. **Size increase compared to follow-up MRI at 1 month due to recurrence. ***Size increase compared to follow-up MRI at 1 month due to ARE.
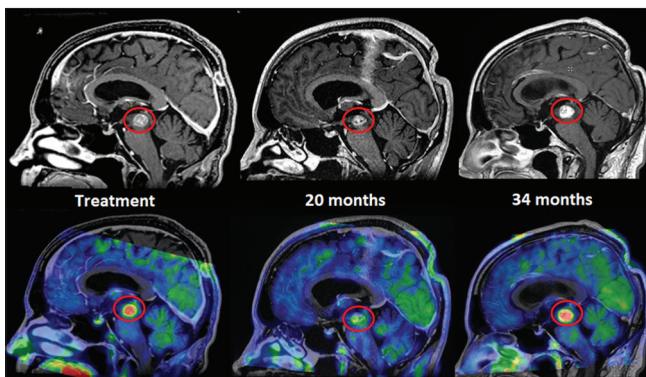

Figure 1: T1-weighted MR- (top row) and Methionine PET images (bottom row), sagittal cross-sections for patient 1. Left: at GKRS 1 (first fraction). Center: Follow-up at 20 months showing tumor volume reduction (MRI) and decreased methionine uptake (PET). Right: Follow-up at 34 months with evidence of tumor regrowth (MRI) and increased uptake (PET). We believe the recurrence was due to insufficient 10 Gy-volume tumor bed coverage (<80%) at GKRS 1 and 2. The areas interpreted as tumor have been highlighted with a thick solid red line

patients who survived less than 6 months (patients 3 and 7, n = 2), no further tumor growth or ARE was reported at the time of the first follow-up; however, effective tumor control could not be confirmed due to the short posttreatment survival time.

Posttreatment tumor volume changes over the follow-up period are illustrated for each patient in Figure 2. Figure 2a shows a significant volume reduction in five of the treated metastases up to the last follow-up. Figure 2b shows the normalized posttreatment volumes of four of the tumors that did not show the same response pattern seen in Figure 2a; in this subgroup, three of the metastases increased in volume secondary to local ARE (patients 2, 4, and 5a), whilst the remaining lesion increased in size due to local recurrence (patient 1).

Mean tumor volume reduction between GKRS 1 and GKRS 3 was −15% and −56% on the MRI at first follow-up (which was planned 4 weeks after GKRS 3, but in two patients could only be performed at 6 weeks

due to scheduling logistics); mean tumor reduction from GKRS 1 to last follow-up was −37%.

Volume reduction estimates at 1 month (compared to last follow-up) are illustrated in Figure 2. All metastases showed an initial volume reduction at first follow-up. Of these, five lesions [Figure 2a] continued to decrease in volume, whereas the remaining metastases either developed ARE or recurrence at later stages. Figure 3 shows treatment and posttreatment MR images for patient 8, illustrating profound volume reduction as late as 19 months after treatment.

ARE developed in four patients (=4 metastases): 2 metastases demonstrated ARE in the form of an increase in contrast-enhancing volume and significant perilesional edema (patients 2 and 4); one metastasis (patient 6) developed new perilesional edema without tumor volume increase. Metastasis 5a remained unchanged until last follow-up MRI at 10 months when a small volume increase with subtle/minimal perilesional edema was identified. ARE development for patients 2, 4, and 6 took place between posttreatment months 4.7 and 5.7 (average 5.4 months), with its peak at 6–10 months after GKRS 1 [Figure 4]. Patient 4 developed the largest treatment-associated edema (estimated at approximately 20 cm³) with its peak at 8 month follow-up [Figure 5]; further details regarding this case and the specifics of ARE diagnosis can be found elsewhere.[76,78]

DISCUSSION

The management of intrinsic brainstem metastases remains a challenge despite major developments in the fields of neurosurgery and oncology. In our opinion, the ideal radiotherapeutic management of brainstem metastases requires the development of more "dynamic" protocols enabling the clinician to utilize a set of algorithms to achieve critically needed, prompt tumor reduction. As previously elaborated, the latter relies on the identification of interactive treatment variables defining clinical suitability and radiosurgical feasibility (see "Materials and methods"
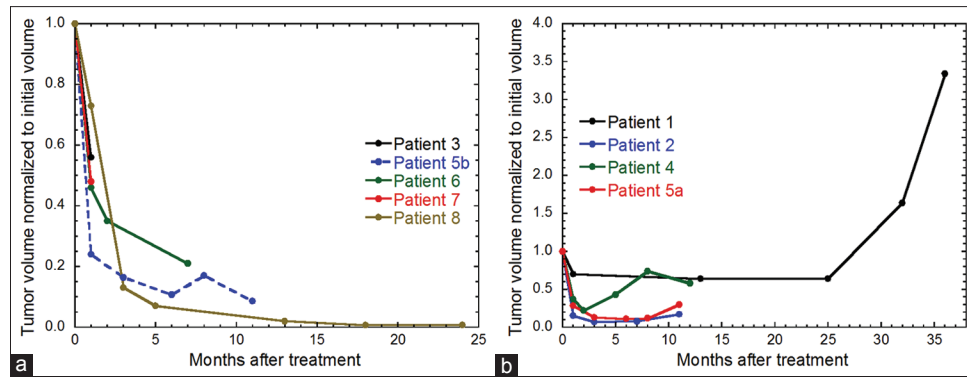
Figure 2: Posttreatment tumor volume dynamics during and after treatment. (a) Monotone/Optimal tumor volume reduction in patients 3, 5b*, 6, 7, and 8. (b) Patients 2, 4, and 5a* show volume increase due to ARE evolvement. Volume increase in patient 1 due to local recurrence (*same patient with two separate brainstem lesions).
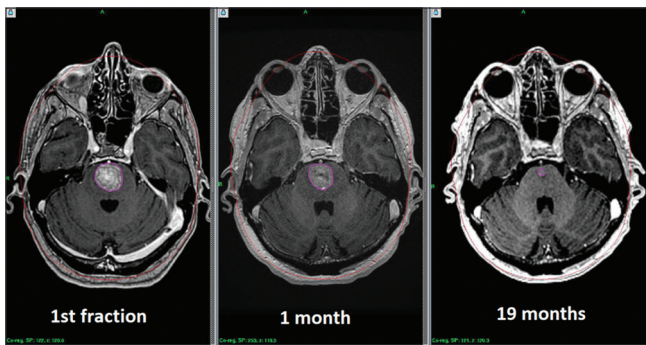

Figure 3: T1-weighted MR images (axial cross-sections) of patient 8. Left: at GKRS 1 (first fraction). Center: Follow-up at 1 month showing slight tumor volume reduction. Right: Follow-up at 19 months with evidence of significant tumor volume reduction. The areas interpreted as tumor have been highlighted with a thick solid red line
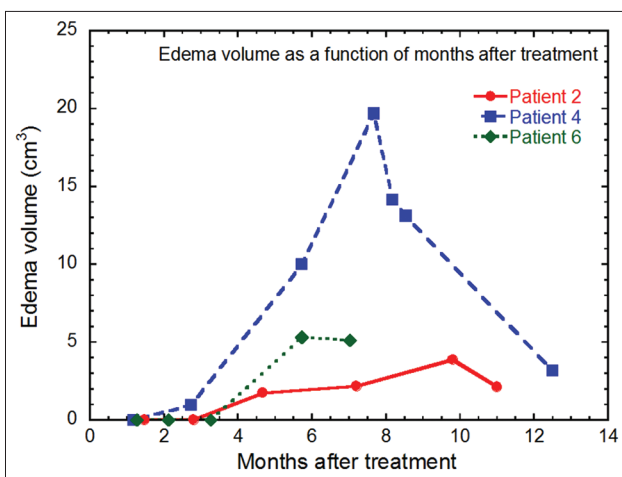

Figure 4: ARE-development in patients 2, 4, and 6: post-3R (measurable) edema volume dynamics. Patient 5a developed minimal (hardly measurable) perilesional edema at last follow-up (10 months) and could not be included in the above figure

section, points 1–6).[1,6,8,28,31,32,36,39,43,48,51,57,67,76,78,85,89] The radiobiological principles of brainstem tolerance have been described elsewhere but warrant to be reemphasized due to their significance.[63] The entire brainstem has a cumulative

radiation tolerance of up to 54 Gy if a conventional fractionation scheme of 1.8–2.0 Gy/day is employed; furthermore, volumes of up to 10 cm^3 (approximately one-third of the brainstem's total volume) may be treated with doses up to 60 Gy using the same fractionation model without major risks for radiation-induced toxicity.[18,54,57,76] Nevertheless, the risk for ARE development seems to increase significantly above a threshold value of 64 Gy; volume-dependent constraints seem less predictive beyond this point.[57] Although conventional radiotherapy schedules seem able to provide some degree of reassurance with respect to healthy tissue tolerance, their efficiency in terms of delivery time and metastatic tumor ablation remains rather limited. On the other hand, single fraction GKRS delivered by gamma knife and other focused radiation modalities have proven effective addressing brainstem metastases;[24,28,35-37,39,42,44,48,50,67,85,86,89] however, ARE evolvement post-radiosurgery remains a concern, particularly in the face of larger lesions.[67] Several studies in brainstem metastatic disease have shown an association of shorter survival and poorer clinical/radiographic outcome with larger tumor volumes (>1 cm^3).[28,35,36,39,42,67] Although a number of studies have reported a low rate of post-single fraction GKRS ARE development in the treatment of brainstem metastases, these results ought to be taken with extreme caution as they may be biased by analytical data describing only serious complications. Furthermore, there may be underreporting of radiation-induced side effects due to short survival times associated with primary disease evolution.[67] Overall, the latter subject remains a matter of debate.

In our experience, the risk of ARE following single fraction GKRS of brainstem metastases is likely to remain low when V_{10Gy} (brainstem) is kept to less than 3 cm^3 and is likely to increase when WBRT or any other form of radiation with local impact has been previously applied. In the latter case, we have set the threshold for post-WBRT–GKRS treatment at V_{10Gy} <1 cm^3. Considering the above, single fraction GKRS may not always be feasible, particularly in
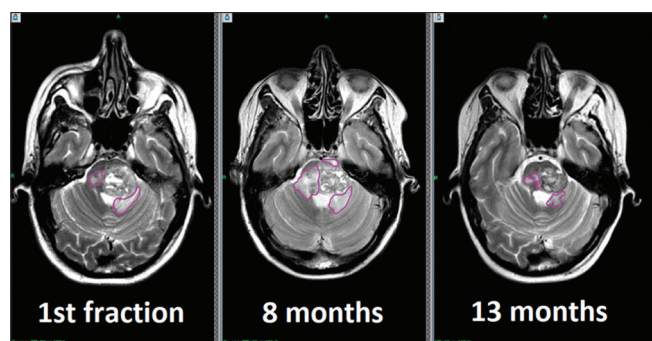
Figure 5: T2-weighted MR images (axial cross-sections) of patient 4. Left: at the first fraction (GKRS 1). Center: Follow-up at 8 months showing peak for edema. Right: Follow-up at 13 months demonstrating significant decrease of edema without corticosteroid treatment. The areas interpreted as edema have been highlighted with a thick solid red line

circumstances of underlying "risk" variables such as prior radiation (such as in cases 4 and 5), "radioresistant" histology (such as in patient 1), and the degree of regional functionality. A number of research groups have reported the benefits of hypofractionated radiotherapy in the management of extra- and intracranial malignant neoplasms.[4,7,15,16,20,21,29,32,33,40,45,48,55,56,58,60,62,63,68,73,76-78,83,87,90] Over the last few years, our group has focused on the use of adaptive hypofractionated radiosurgery on critically located metastatic lesions, including brainstem lesions.[76-78] As a summary, the proposed 3R technique is based on a series of image-guided, dynamic GKRS interventions aiming to adapt peripheral prescription doses and subsequent intratumoral escalating dose distributions to changing tumor volumes during the week of treatment.[76,77,78] Trying to keep dose distributions to healthy tissues to a "constant minimum" while increasing the marginal dose at each GKRS is a crucial aspect of this surgical intervention. When applied in the acute/subacute setting, this technique allows prompt tumoricidal effects whilst limiting the risk for ARE development.

As in our case series, hypofractionated schedules (including 3R) may offer a tangible solution, at least equally effective as single fraction GKRS in terms of tumor control, whilst decreasing the risk of associated ARE.[76,78,90] But how do we extrapolate the above information onto an effective radiosurgical regimen in the context of the brainstem? Although the latter question remains a topic of considerable deliberation, we believe the answer may rest in the methodical integration of specific treatment feasibility variables and their projection onto well-known linear quadratic model-based biological effective dose conversions[15,16,19,20,32,34,62,72,73,75,76] in order to trigger specific biological processes such as reoxygenation, optimization of perfusion kinetics, DNA repair, and radiation-triggered immune responses. The latter hypothesis seems to match suggestions and findings reported by other groups[5,10,30,41,70,76,79] and will be further discussed elsewhere.

In this study, major challenges at GKRS 1 were identified as a history of previous WBRT (seen in two patients: 4 and 5) and underlying edema in five other patients (patients 1, 4, 6, 7, and 8) which could theoretically increase the risk for ARE. Having anticipated the above, 3R treatments were strategically conceptualized by outlining crucial "ablative" isodose lines primarily on intratumoral contrast-enhancing areas (set at 10, 12, and 15 Gy) whilst keeping radiation dissipation within the 5-Gy-isodose line as constant/homogeneous as possible at each GKRS session. Although four patients developed some evidence of ARE after 3R treatment, we could not correlate the presence of edema at GKRS 1 with radiation-induced toxicity and neurological impairment as all patients remained nearly asymptomatic up to their last follow-up. Based on our experience, we believe clinicians should aim to cover at least 70% of the tumor bed with the 10-Gy isodose unless the patient has previously been treated with radiation; these thresholds should be increased (>80%) in cases of radioresistant histologies. Studies correlating the effects of high dose per fraction (>8–10 Gy) to specific antitumoral responses (improvement of oxygen and perfusion kinetics, induction of tumoral vascular damage, and enhancement of cytotoxic T-cell activity among other traits) seem to provide a rationale to this line thinking.[5,10,60,70,75-77] However, more studies are warranted to confirm the latter.

As pointed out earlier, we intended to include patients in RPA classes 1 and 2 as best overall survival times are expected in these groups.[25,26,28,43,51,52,88] However, with the intent of compassionate treatment to prevent severe neurological impairment, two other patients in RPA class 3 were also treated with our regimen and are included in this cohort. Due to the small number of patients included in this study, we found no correlation between RPA classes and best response or ARE frequencies. Yet, taking into consideration the available medical literature, we believe RPA classes and underlying histology should still be considered as relevant prognosticators.[25,26,28,43,51,52,88]

Advanced age and comorbidity have also been suggested to have a negative impact in terms of focal therapy efficiency and expected clinical outcome; the studies of Debus *et al.*, relating brainstem tolerance to high-dose radiation of skull base tumors, suggested that vascular morbidity and prior skull surgery could potentially affect regional brainstem tolerance thresholds.[12,76] Yet, despite a number of studies addressing this (some including the Charlson Comorbidity Index), the impact of comorbidity on cranial surgery and brain radiotherapy remains a topic of discussion and warrants further investigation, particularly in the context of hypofractionation[14,17,22,49,64,74] With respect to our study, three patients (3, 6, 7) had some degree of vascular disease (mainly hypertension); longer survival was observed in patients with less comorbidity, regardless of age (patients

1, 2, 4, 5, and 8). Careful conclusions are to be drawn in this context due to limited number of patients.

As described in our cases, hypofractionated regimes (including 3R) are not free from ARE and tumor recurrence/persistence may also occur. Optimal pretreatment diagnostics and reliable interpretation of post-GKRS high-performance neuroimaging (incl. PET) remain essential[61,66,82] to differentiate between viable tumor and ARE (e.g. necrosis) as the cause of increase in lesional size, perilesional edema, and contrast enhancement at post-radiation follow-up. This was particularly the case for patient 1 in whom MR perfusion was limited by susceptibility artifact and small lesion size, requiring CT-perfusion and 11C-metionine amino acid PET to verify recurrence and patient 4 with a more conclusive MRI and PET-verified ARE. Multiple studies demonstrate the usefulness of advanced MR techniques such as MR perfusion and diffusion for the evaluation of posterior fossa lesions.[27,35,53,71,81] The presence of increased rCBV on MR perfusion[3,11,13,38] with high uptake on amino acid PET such as 11C-methionine[11,13,38,59,78,80,82] as well as the cautious interpretation of local restricted diffusion[2,46] support the diagnostic assessment of viable/evolving malignant tumor, whilst their absence provides support for ARE diagnosis. More technical details and information on the number of publications addressing these aspects can be found elsewhere.[76,78]

Although 3R seems a promising tool in the acute management of metastatic brain lesions, its use in "single"/ non-concomitant settings may not be enough to trigger its true potential. As pointed out in our results, recurrence may be identified at a later stage, particularly in cases of rather radioresistant histologies and/or in long-term primary tumor survivors. The latter was the case for patient 1 where initial tumor reduction was followed by a period of "stable imaging" until focal relapse was identified/confirmed at 34 months after treatment completion after the treatment. Moreover, even with good local tumor control post-3R (at short and long term), issues concerning distant metastatic activity may potentially decimate all achievements made from successful focal treatment and calls for a more comprehensive immunological / oncological approach addressing the containment of the primary tumor or distant, non-CNS, metastases.

Overall, 3R treatment provides particular advantages: (1) it implements a rapid salvage plan with preservation of neurologic function and (2) generates a time window to customize further treatments targeting specific intra- and extracranial responses. In this context, immune-mediated mechanisms aiming to synergize and expand the effects of ionizing radiation on local/distant sites as well as the recognition and use of antigen-based biomarkers predicting response and survival have been of utmost interest.[69,91] The latter will lead to further studies in the near future.

CONCLUSION

In this study, sequential GKRS treatment according to our proposed 3R regimen proved effective in the management of brainstem metastases in terms of local tumor control and limited radiation-induced toxicity/ARE. Treatment was customized based on high performance imaging, relevant clinical information, dose-volume data, and regional dose constraints. In the context of available data, the presence of perilesional edema should be taken seriously but its presence should not prevent the patient from receiving further radiation therapy in stereotactic conditions. Steroid coverage during the period of treatment and at follow-up should be customized in harmony with symptomatic evolution. Based on the available medical literature, we believe that intrinsic radiobiological factors such as tumor radiosensitivity and optimized oxygenation/perfusion kinetics might have played an essential role on treatment outcome. Further prospective studies with larger number of patients are warranted.

Abbreviations
3R (Rapid Rescue Radiosurgery), RPA (recursive partitioning analysis), ARE (adverse radiation effect), MRI (magnetic resonance imaging), GTV (gross tumor volume), PTV (planning target volume), WBRT (whole brain radiation therapy).

Conflicts of interest
There are no conflicts of interest.

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