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Original Article

The concept of rapid rescue radiosurgery in the acute management of critically located brain metastases: A retrospective short-term outcome analysis

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Abstract

Background: Adaptive hypofractionated gamma knife radiosurgery has been used to treat brain metastases in the eloquent regions while limiting the risk of adverse radiation effect (ARE). Ablative responses might be achieved within days to weeks with the goal to preserve the neurological function. The application of this treatment modality in selected acute/subacute settings has been termed Rapid Rescue Radiosurgery (RRR) in our department. We report the expeditious effects of RRR during treatment and 4 weeks after treatment completion.

Methods: In all, 34 patients with 40 brain metastases, each treated over a period of 7 days in three separate gamma knife radiosurgery sessions (GKRS 1-3) between November 2013 and August 2017, were retrospectively analyzed in terms of tumor volume reduction, salvage of organs at risk (OAR), and radiation induced toxicity under the period of treatment (GKRS 1-3 = one week) and at first follow-up magnetic resonance imaging (MRI) (4 weeks after GKRS 3).

Results: Mean tumor volume at GKRS 1 was 12.8 cm3. Mean peripheral doses at GKRS 1, GKRS 2, and GKRS 3 were 7.7 Gy, 8.1 Gy, and 8.4 Gy (range: 6.0-9.5 Gy) at the 35% to 50% isodose lines. In the surviving group at first follow-up (n = 28), mean tumor volume reduction was – 10% at GKRS 3 (1 week) and – 48% four weeks after GKRS 3. There was no further clinical deterioration between GKRS 3 and first follow-up in 21 patients. Six patients died prior to first follow-up due to extracranial disease. No ARE was noticed/reported.

Conclusions: In this study, RRR proved effective in terms of rapid tumor volume reduction, debulking, and preservation/rescue of neurological function.

Key Words: Adaptive hypofractionation, adverse radiation event, brain metastases, gamma knife radiosurgery, recursive partitioning analysis

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INTRODUCTION

The management of large brain metastases in or near eloquent brain remains a major challenge in the field of neuro-oncology. These life-threatening lesions often lead to prompt and severe neurological impairment. Their acute and subacute management is difficult, particularly with underlying metachronous/synchronous metastatic activity. In addition, recursive partitioning analysis (RPA)–surrogate factors may limit safe surgical removal and optimal postsurgical focal cavity radiation. Chemotherapeutic approaches are deemed of low efficacy due to blood-brain barrier constraints. Despite promising advances in the field of immunotherapy, exemplified in the ascent of check point inhibitors, there are limited data on the efficacy of immunotherapeutic approaches in the treatment of brain metastases.[38] Radiation therapy with or without prior microsurgery plays a major role in the management of brain metastases. Once considered an acceptable treatment option, whole brain radiation therapy (WBRT) is increasingly avoided due to both inadequate control of large/radioresistant brain metastases and to impairing neurological side-effects including decline in memory and learning;[3,38,48] alternatively, single fraction radiosurgical approaches have emerged as a viable treatment alternative, offering optimal local control rates while deferring or avoiding WBRT and maintaining a good quality of life.[21,27,28,30,46]

However, single fraction radiosurgery may not be feasible in the face of large metastases due to the risk of adverse radiation effect/event (ARE) development, particularly in eloquent brain. Several reports have presented stereotactic hypofractionation as an alternative to single-fraction radiosurgery, retaining comparative local control with reduced risk of ARE.[11-13,17-20,22,23,33,36,40,41,50] Cases of prompt ablative results on large, aggressive, and eloquently located unresectable lesions using adaptive hypofractionated gamma knife radiosurgery have previously been reported.[43,44,51] The conceptual use of this hypofractionated radiosurgical technique in the management of intractable metastases in selected acute/subacute settings has been coined at our institution as Rapid Rescue Radiosurgery (RRR).[43,44]

The aim of this first series study is to analyze the effects of RRR in terms of tumor volume reduction dynamics and ensuing decompression during the time of treatment (7-day period) and at 4 weeks after treatment completion.

MATERIALS AND METHODS

Between November 2013 and August 2017, 34 consecutive patients with 40 cerebral metastases were treated with RRR at our center, the Gamma Knife Unit, Department of Neurosurgery, Karolinska University Hospital, Stockholm. In all cases, the lesions were deemed not suitable for microsurgery, systemic therapy, or other form of radiotherapy. We conducted a retrospective analysis of all medical records and corresponding imaging (treatment and follow-up), including LGP (Leksell GammaPlan) volume data. RRR was stratified in two fields: (i) brainstem radiosurgery which included intrinsic and extrinsic brainstem lesions (B-RRR) and (ii) nonbrainstem radiosurgery (NB-RRR), consisting of intra- and extra-axial metastatic lesions, including dural metastases and focal *leptomeningeal* metastases. In this study, RRR was applied in the metastatic lesions assessed as "large" and hence not suitable for single fraction gamma knife radiosurgery (SF-GKRS). Traditionally, metastatic lesions have been volumetrically defined as "large" based on straightforward mathematical calculations (generally, >30 mm in diameter and/or >8-10 cm in volume^3) regardless of the focal topographic conditions. In the context of RRR settings, the definition of tumor "largeness" was dynamically assessed by considering a number of factors: (i) dose volume estimates at pretreatment and at GKRS 1 (intra- and extra-tumoral dose distributions in relation to the single and multiple fraction treatment), (ii) LQ model–based isoeffective dose conversions, and (iii) treatment feasibility variables (TFV). The latter variables were identified as follows:

1. Affected brain regions: degree of regional eloquence and corresponding neurologic function
2. Location and the number of organs at risk
3. Presence of perilesional edema
4. Prior radiation therapy with potential/synergic impact on future ARE-evolvement, particularly the brainstem
5. Degree of response to prior intra- and extracranial radiotherapy (identifying dose requirements in relation to expected response)
6. Histopathology and corresponding degree of radiosensitivity/radioresistance
7. RPA-surrogate factors.

Inclusion criteria

Brainstem radiosurgery group (B-RRR): Intrinsic and extrinsic brainstem metastases with or without perilesional edema, with or without fourth ventricle (V4) compression, and the following preexisting conditions:

(i) Patients not candidate for microsurgery, other form of radiotherapy, or systemic (single or concomitant) treatment.

(ii) Metastases assessed not suitable for SF-GKRS when V_{10Gy} >1 cm^3 applying a peripheral prescription dose of 16-18 Gy (single fraction) with prior radiotherapeutic focal impact (including WBRT) or V_{10Gy} >3 cm^3 without previous radiotherapy. Dose per fraction assessed by underlying TFVs and structured adaptively in relation to volume kinetics.

(iii) Karnofsky performance status (KPS) at least 70 and RPA of 1 to 2 when possible. However, exceptions were considered (KPS <70, RPA 3) in cases of CSF-pathway compression (such as V4 compression) requiring acute salvage of the neurological function and/or avoidance of impending neurological death ("compassionate" treatment).

Non-brainstem radiosurgery group (NB-RRR): Metastases with critical location outside brainstem boundaries with or without perifocal edema, with or without CSF pathway compression, with the following preexisting conditions:

(i) Patients not candidate for microsurgery, other form of radiotherapy, or (single/concomitant) systemic treatment targeting the intracranial lesion(s) at hand.
(ii) Metastases requiring a peripheral dose of 18 Gy or more but not suitable for single dose gamma knife radiosurgery due to large volume (>8-10 cm^3). Smaller volumes (<8 cm^3) were still assessed as "large" depending on preexistent TFVs (previously described). Dose per fraction assessed by underlying TFVs and structured adaptively in relation to the volume kinetics.
(iii) KPS at least 70 and RPA of 1 to 2. Exceptions were considered (KPS <70, RPA 3) in cases aiming to avoid further neurological deterioration (compassionate treatment).

Treatment settings

RRR-treatments consisted of three separate GKRS sessions (GKRS 1-3) delivered over a period of 7 days. The Leksell Coordinate Frame G (Elekta AB, Stockholm, Sweden) was mounted under local anesthesia. The three separate stereotactic magnetic resonance imaging (MRI) examinations for gross tumor volume (GTV) delineation included precontrast T1 and T2 weighted sequences and post gadolinium (40 mL IV Dotarem 279.3) 3D T1 weighted sequences on the GE Discovery MR450 1.5T MR [Table 1]. Due to frame-fixation, no margins were added to the GTV. First follow-up MRI was planned 4 weeks after GKRS 3 pre and post gadolinium (20 mL IV Dotarem 279.3); the majority of follow-up scans were performed at our institution. Follow-up MRIs performed at referring institutions were subsequently reviewed at our center. Our study included all patients having completed RRR treatment with or without survival to first follow-up MRI at 4 weeks. Patient characteristics are summarized in Table 2.

Thirty-four patients completed the treatment and were included in our analysis [Table 3]. One patient was not able to complete treatment due to severe neurologic deterioration due to aggressive focal tumor growth despite ongoing RRR treatment and was therefore excluded from the statistical analysis. Overall, there were 20 men and 14 women aged 41 to 87 years (mean: 63 years). The primary tumor was of lung cancer origin in 12 cases followed by breast cancer (n = 7), colorectal cancer (n = 6), malignant melanoma (n = 4), mesothelioma (n = 2), thymus carcinoma, and ovarian and renal cancer (n = 1 in each group) [Table 2]. Twelve patients had ongoing systemic treatments at the time of inclusion. Seven patients had WBRT prior to RRR. Three patients had previously been treated (for a different metastasis) with a LINAC-based hypofractionated schedule of 6 Gy × 5 (without prior WBRT), one of which overlapped with a RRR-treatment planning of a left-sided temporal lesion. Smaller, co-existing metastases outside RRR-treatment field boundaries were treated by means of SF-GKRS and scheduled at the same time as RRR's GKRS 1. All patients but three had ongoing cortisone treatments due to edema surrounding their lesions. The KPS score at GKRS 1 was at least 70 in 31 patients. Most patients were in RPA-Class 2 (25 patients) while only three patients were in RPA Class 1. The mean dose administered at GKRS 1, 2, and 3 was 7.7 Gy, 8.1 Gy, and 8.4 Gy, respectively. The minimal prescribed dose at the margin was 6 Gy and the maximum was 9.5 Gy. The prescription isodose varied between 35% and 40% in almost all cases. Treatment settings are summarized in Table 4.

Table 1: Summary of imaging protocol

Type of imaging and corresponding characteristics
Stereotactic (treatment) MRI: MRI performed at a single site tertiary care university hospital on GE Discovery MR450 1.5T. Sagittal SE T1, axial CE T1 FSE, CE 3D T1 weighted FSPGR with multiplanar reconstruction and high definition imaging T2 (T2 propeller, FLAIR, FIESTA with cerebello-pontine angle locations)
Follow-up MRI: including T1 and T2 precontrast, axial CE 3D T1 (actual sequences depending on site of follow-up, with all images reviewed by our team)*
Follow-up PET: in case of clinical question of recurrence/progression: 30 minute scan in 3D mode

*RRR: Imaging protocol summary. Follow-up MR on one patient was performed without IV contrast medium due to renal failure and the tumor contours were measured on the unenhanced T1-images

Table 2: Patient and treatment parameters

Average age (years)	63
No. patient >60 years	20 (59%)
Primary tumors (no. of patients/%)	Lung (12/35%) Breast (7/21%) Colorectal (6/18%) Malignant melanoma (4/12%) Mesothelioma (2/6%) Thymus carcinoma, renal, and ovarian cancer (3/9%)
Number of metastasis >1	22 (65%)
Brainstem location	12 (30%)
Non-brainstem location	28 (70%)

Table 3: Tumor volume at GKRS 1 and peripheral prescription doses (GKRS 1-GKRS3) for each lesion treated with RRR

Age	Initial tumor volume (cm^3)	Prescribed dose (Gy)		
		GKRS 1	GKRS 2	GKRS 3
41	9.2	6.0	6.0	7.0
78	7.1	8.0	8.0	8.0
54	1.4	8.0	8.0	8.5
64	5.2	7.5	7.5	8.5
74	2.9	8.0	8.5	9.0
64	3.0	8.0	8.0	8.5
50	25.0*	8.0	8.5	8.5
	14.5*	8.0	8.5	9.0
	2.1*	7.5	8.0	8.0
60	29.8	8.0	9.0	9.0
67	15.1	8.5	8.5	9.0
72	17.3	8.0	8.5	9.0
61	4.8	7.0	7.0	8.0
48	9.2	7.5	8.0	8.5
73	10.3	8.0	9.0	9.0
73	9.5	7.5	8.0	8.0
76	10.2	8.0	8.5	9.0
71	1.8	8.0	8.5	8.5
56	12.0*	8.5	8.5	9.5
	17.3*	8.5	8.5	9.0
62	22.2*	7.5	8.0	8.0
	9.4*	7.5	8.0	8.0
68	25.1	8.0	8.0	8.5
51	0.3*	7.0	8.0	8.0
	0.5*	7.0	8.0	8.5
46	3.7	6.0	6.5	7.0
57	32.5	6.0	6.0	6.0
74	10.2	7.5	8.0	8.5
53	7.4	8.0	9.0	9.0
65	20.0	6.5	7.0	7.5
58	19.4	8.0	8.0	9.0
52	3.9	7.0	7.5	8.0
50	17.2	8.0	8.5	9.0
87	24.0	8.0	8.5	8.5
63	13.8	6.0	6.5	7.0
54	12.9*	8.5	9.0	9.0
	3.6*	8.5	9.0	9.0
59	9.2	8.5	9.0	9.5
64	18.0	7.5	8.0	8.5
82	50.1	8.5	9.0	9.0

*Same patient

Table 4: Summary of treatment settings

Treatment stages	Characteristics
Tumor "largeness" assessment at pretreatment	Tumor largeness not only defined according to "fixed" threshold measurements (30-mm threshold) or constant volume criteria (8-10 cc thresholds) but also dynamically assessed according to the field of surgery (brainstem vs non-brainstem) and preexisting treatment feasibility variables
Treatment planning based on high performance imaging and dose adaption	Stereotactic MRI prior to each GKRS [Table 4] to adapt radiation delivery to target kinetics: Tumor volume reduction at each fraction leads to further prescription marginal dose augmentation and optimization of dose distribution inside and outside target
Follow up schedule	First follow-up MRI scheduled 4 weeks after treatment completion to assess post-RRR subacute tumor ablative dynamics.

RRR: Settings summary

RESULTS

Clinical outcome

Twenty-eight patients with 33 lesions were able to undergo their first follow-up MRI at 4 weeks posttreatment. The remaining six completed treatment but died prior to their first follow-up due to extracranial complications including a suspected cardiac arrest in one patient and systemic disease progression in the remaining five. No clinical evidence of radiation-related side-effects was reported in the latter group. The median KPS was stable during the course of the treatment. Of the surviving 28 patients evaluated at 4 weeks after treatment completion (first follow-up MRI), there was a clinical KPS-improvement in eight patients, while 13 patients remained stable. Seven patients experienced KPS-deterioration, although not RRR-related. All patients except three had cortisone treatment at the time of RRR-treatment due to the presence of peritumoral edema. Cortisone treatment was withdrawn prior first follow-up MRI in five patients. The remaining patients had ongoing cortisone at the time of their first follow-up. The RPA of patients who were initially in Class 1 at the time of inclusion (n = 3) remained unchanged at 4 weeks after treatment completion. Among the 25 patients with initial RPA Class 2 (still at the time of inclusion), 15 remained in the same class, 3 patients improved to Class 1, 3 patients deteriorated to Class 3 at first follow-up, while the rest died before the first follow-up. Six patients had an initial RPA class of 3, two of them died of extracranial tumor progression before the first follow-up MRI; among the surviving four patients, two remained in the same class and two patients improved to RPA Class 2 due to KPS-increase [Table 5].

Radiological outcome

Initial mean tumor volume at GKRS 1 was 12.8 cm^3 (range: 0.3-50.1 cm^3). Tumor volume reduction during the course of RRR was −6% and −10% at GKRS 2 and GKRS 3, respectively. Mean tumor volume at the first follow-up was available for 33 lesions (28 patients). Average mean tumor volume (at the first follow-up MRI)

Table 5: RRR-treatment outcome analysis in terms of lesion volume dynamics

Age	Sex	N of mets	Histology	Localization	Δv (%) GKRS 3	Δv (%) 1 month	RPA initial/at 1 month
41	F	Multiple	Lung	Brainstem	−17	−63	1/1
78	M	Multiple	Lung	Brainstem	7	−52	2/3
54	M	Single	Melanoma	Brainstem	−22	−7	½
64	F	Single	Breast	Brainstem	−5	−27	2/2
74	F	Multiple	Breast	Brainstem	−16	−85	2/2
64	F	Multiple	Lung	Brainstem	−3	NA	2/NA
50	M	Multiple	Thymus	Temporal lobe	24	−93	1/1
				Parietal lobe	−8	−94	
				Temporal lobe	6	16	
60	M	Multiple	Lung	Parietal lobe	−1	−70	2/2
67	M	Multiple	Melanoma	Cerebellum	−9	−41	2/2
72	F	Single	Caecum	Cerebellum	−1	−17	2/2
61	F	Single	Ovary	Brainstem	6	−60	3/2
48	M	Multiple	Lung	Temporal lobe	−66	−91	2/2
73	M	Single	Lung	Frontal lobe	−8	NA	3/NA
73	F	Single	Lung	Thalamus	−10	NA	3/NA
76	M	Single	Mesothelioma	Brainstem	−23	−50	3/3
71	F	Multiple	Lung	Brainstem	−15	−30	2/3
56	M	Multiple	Renal	Central	1	−9	2/2
				Frontal lobe	−8	−34	
62	M	Multiple	Sigmoid	Cerebellum	22	NA	2/NA
				Temporal lobe	9	NA	
68	M	Single	Mesothelioma	Parietal lobe	−1	−24	3/3
51	F	Multiple	Breast	Brainstem	−9	−53	2/2
				Brainstem	−33	−52	
46	F	Multiple	Breast	Brainstem	−35	−84	2/1
57	M	Single	Lung	Occipital lobe	19	−72	1/1
74	M	Single	Lung	Temporal lobe	−45	NA	2/N/A
53	F	Multiple	Breast	Motor region	−16	−60	1/1
65	M	Single	Lung	Frontal lobe	−22	−33	2/2
58	M	Multiple	Melanoma	Occipital lobe	34	−23	2/2
52	M	Multiple	Lung	Thalamus	−9	NA	2/N/A
50	M	Multiple	Melanoma	Occipital lobe	−29	−63	2/2
87	M	Multiple	Rectal	Fronto-parietal lobe	1	−22	2/2
63	F	Multiple	Breast	Cerebellum	−32	−48	2/2
54	F	Multiple	Rectal	Cerebellum	−14	−28	2/3
				Cerebellum	−19	−61	
59	M	Multiple	Colorectal	Cerebellum	−11	−48	2/2
64	F	Multiple	Breast	Cerebellum	−23	−64	2/2
82	M	Single	Colorectal	Occipital lobe	−7	−36	2/2

(=Δv) and RPA-evolution at 1 week (GKRS 3) and 4 weeks posttreatment (first follow-up MRI). NA (In grey) = Not available due to death prior first follow-up

was 6.0 cm^3, ranging between 0.1 and 32 cm^3, representing an average reduction of −48% (between GKRS 1 and first follow-up MRI posttreatment) [Table 5]. With regard to perilesional edema [Table 6], all patients but one presented measurable improvement of edema at first follow-up. Mean volume of edema, as evaluated on T2-weighted sequences, was 43.1 cm^3 at GKRS 1, and 11.9 cm^3 at first follow-up MRI [Table 6].

DISCUSSION

RRR from a historical perspective

The management of brain metastases in acute and subacute settings remains complex and requires tailored treatment.[43,44] Microsurgery followed by radiation delivery to the surgical cavity remains the cornerstone of brain metastasis management in terms of local recurrence

Table 6: Perilesional edema dynamics at each fraction and at 1 month follow-up

Pat no.	GKRS1	GKRS2	GKRS3	First follow-up (4 weeks post-treatment)
7	45.4	58.4	68.2	2.9
8	28.2	28.7	31.8	5.2
12	120.8	102.2	91.4	1.9
17	23.2	21.4	24.8	9.8
19	38.5	28.1	30.2	23.6
23	73.8	73.8	66.3	NA
25	16.4	19.3	20.1	7.4
26	91.1	67.0	54.9	15.4
27	23.1	25.4	26.4	NA
29	40.3	39.4	45.9	51.5
31	3.7	2.3	2.4	0
32	12.8	15.4	16.1	1.5

Volume of perilesional edema (cm^3) at each fraction and at 1 month follow-up. At GKRS 1, 30 out of 34 patients had ongoing corticosteroid treatment due to the targeted lesion; yet, 12 had significant perilesional edema. At first follow-up, edema had decreased significantly in all patients but one (patient 29); at this stage, 25 were still on corticosteroid treatment though their intake had decreased dramatically and was not clinically related to the treated lesion, including patient no. 29

free survival.[9,38] Upfront or adjunctive systemic treatments (immunotherapy, alternatively chemotherapy) may also be considered in selected patients.[38] Yet, in many cases, microsurgery may not be feasible due to the critical decisive factors, such as difficult topographic conditions, concomitant number of brain metastases, and complex clinical elements (primarily KPS/RPA and comorbidity). In this context, SF-GKRS has proven effective for small metastatic lesions.[28,30,46] However, the effectiveness of SF-GKRS in the management of "larger" unresectable metastases (generally, >30 mm/8-10 cm^3) remains a topic of vivid discussion as the risk for AREs is believed to become more significant.[46] In many such cases, WBRT and local hypofractionated radiation treatments are often considered.[5,38,48] However, WBRT is increasingly being avoided due to the unacceptable risk for neurotoxicity, particularly in long-term survivors.[3,5,18,38,46,48] As a consequence of the shift away from WBRT, hypofractionated schedules delivered by means of LINAC-based instruments, proton beam devices, or gamma knife equipment (among others) are increasingly being used in the management of intractable brain metastases as they enable the clinician to achieve tumor control while limiting the risk of ARE.[11-13,17-20,22,23,33,35,36,40,41,43,44,46,50]

Different groups have reported the application of hypofractionated gamma knife radiosurgery in the management of large brain metastases,[23,33,50] including a particular technique known as adaptive radiosurgery;[43,44,51] when applied in well-defined acute and subacute settings, this image-guided procedure allows the surgeon to deal with life-threatening, neurologically destructive neoplasms in almost real-time conditions, achieving in many cases next to comparable debulking/decompressive surgical results during the course of treatment (days) and at postsurgery (weeks). The principle lies in dynamically adapting peripheral prescription and tumor bed dose distributions to ongoing tumor volume reduction at each GKRS with almost surgical precision while trying to withhold/minimize dose dissipation to healthy brain tissues as much as possible. The result is a set of well-conceived intratumoral heterogeneous/escalating dose distributions which will subsequently lead to rapid ablative denouement in most cases [Figures 1-3].[43,44] This concept is known at our institution as Rapid Rescue Radiosurgery.

Eligibility for RRR-treatment is not solely determined by simple, fixed lineal measurements but by the combination of co-existent TFVs and LGP-based GTV estimations. For instance, depending on topographic conditions (such as absence of edema and degree of regional eloquence among others), RRR-treatment thresholds for lesions located outside the brainstem can be set on "standard" volumetric estimates above (GTV >8-10 cm^3); yet, smaller metastases (GTV <8 cm^3) may be subjected to RRR to avoid SF-GKRS-induced toxicity such as in the case of lesions harbored in highly functional areas.[43,44] In the case of brainstem lesions, RRR settings are much more tailored and complex due to the brainstem's unique anatomical, neuro-physiological, and radiobiological traits; treatments are conceived by combining particular dose-volume estimates with preexistent TFV's, balancing volume-dependent radiotolerance thresholds required for tumor ablative prescription doses.[44] In this study, treatment schedules of three GKRS delivered over the course of 7 days were deemed necessary to (i) achieve necessary ablative results, (ii) limit unnecessary dose dissipation to normal tissues, (iii) accommodate logistics associated with stereotactic imaging requirements (one MRI prior to each GKRS), (iv) minimize frame applications (one frame mounting prior to each GKRS), and (v) fine tune treatment according to reported radiobiological factors with potential impact on local tumor microenvironment and normal brain tissue (OAR included) such as reoxygenation, perfusion, repair, and radiosensitivity.[1,2,6-8,25,26,41,42,45]

Over the years, the RPA classification of brain metastases has been widely used as a prognostic model of treatment response and survival;[15, 37] aiming to match world medical data in that respect, we included primarily patients with a KPS of at least 70 (70-100) and RPA of up to 2 (1-2). However, in this study, we found no strong correlation between RPA classes and best tumor response, probably due to the limited number of patients included and the restricted period of time analyzed for the purpose of this study.

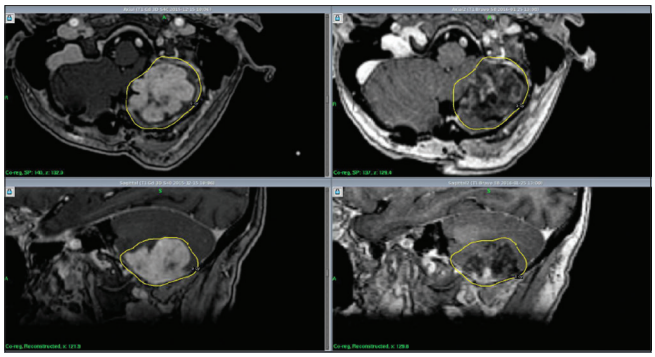

Figure 1: MRI (CE 3D T1): Axial and sagittal cross-sections (left to right) illustrate decreasing tumor volume of an infratentorial metastatic lesion from GKRS 1 (left) to first follow-up MRI 4 weeks after GKRS 3 (right)

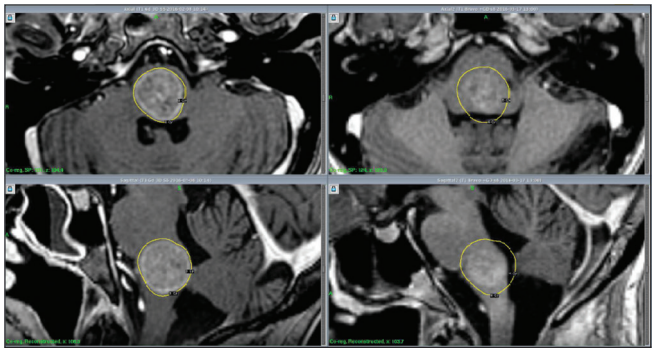

Figure 2: MRI (CE 3D T1): Axial and sagittal cross-sections (left to right) illustrate decreasing volume of a brainstem metastasis with ensuing fourth ventricle normalization from GKRS 1 (left) to first follow-up MRI 4 weeks after GKRS 3 (right)

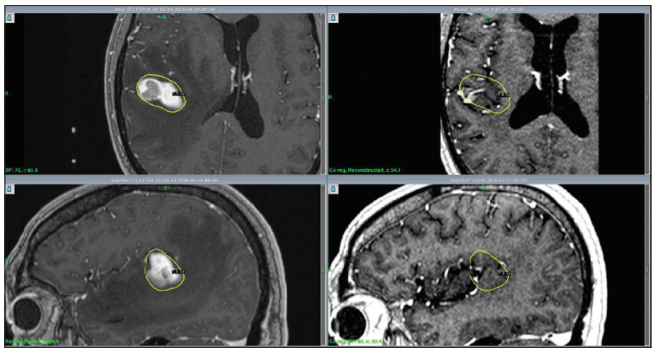

Figure 3: MRI (CE 3D T1): Axial and sagittal cross-sections (left to right) illustrate decreasing tumor volume and perilesional edema of a supratentorial metastatic lesion from GKRS 1 (left) to first follow-up MRI 4 weeks after GKRS 3 (right)

The role of LQ-formalism in RRR-planning

Initial prescription dose at GKRS 1 and MRI-guided peripheral dose augmentation (with subsequent intratumoral escalating dose distribution at GKRS 2 and 3) were conceived by applying LQ-based biologically effective dose (BED) estimates normalized to hypofractionated regimens known to provide local tumor control and limited risk for ARE development. These "reference" schedules ranged between 6-7 Gy × 5 and 7-10Gyx3.[4,13,18-20,36,43,44,46] Prescription doses to tumor margins were set at lower isodose lines (usually at the 35%-40% lines) to (i) match local target conformity aspects, (ii) increase the average dose inside the tumor, and (iii) optimize 10 Gy-volume increment at each GKRS. Taking into account the possible limitations of the LQ-formalism, isoeffective conversions[1,26,41,42] were used to (i) identify bearable/minimally toxic biologically effective dose distributions outside tumor margins using an alpha/beta ratio of 2-2.5 for normal brain tissue and (ii) set a customized Baseline Ablative Isodose Line (BAIL) adjusted to the tumor's potential alpha/beta ratio. We have defined BAIL as the minimum physical/biological dose required inside the tumor to trigger ablation. Assuming BED-calculations provide reliable estimates up to 8 to 10 Gy per fraction (=per GKRS), isoeffective schedules were mainly conceived to balance expected dose-volume dependent tumor responses to potential dose-volume related ARE-development.[1,41,42] As a result, the BAIL was generally set at 10 Gy covering at least 70% to 80% of the tumor bed while prescription doses were adjusted to healthy tissue tolerance requirements.

BAIL: Microenvironmental rationale

Some studies seem to support our line of reasoning;[41,42] in this particular context, it is crucial to consider that the effects of radiation on tumor and normal tissue microenvironment are technically dependent on (i) dose per fraction, (ii) correspondent delivery schedule, and (iii) availability and correct interpretation of high-performance imaging. In the context of the first two factors, there may be an underlying relation between high dose per fraction (particularly above 10 Gy thresholds) and crucial environmental changes involving prompt oxygen responses and local perfusion dynamics.[2,6,7]

As early as 2000, Bussink *et al*. described how hypoxia decreased while perfusion promptly increased by treating squamous cell carcinoma with 10 Gy.[2] Crokart *et al*. (2005) reported that oxygen concentrations in the interstitial space peak about 3 to 4 hours after local delivery of 10 Gy and remain increased for a further 24 hours. The group suggested that an immediate inflammatory response and a decrease in oxygen consumption could contribute to the loss of tumor hypoxia and focal perfusion increment.[8] A study on rectal carcinoma by Janssen *et al*. (2010) reported a CT and DCE-MRI-verified increase in tumor perfusion after applying 5 Gy × 5, suggesting an improved bioavailability of cytotoxic agents administered after the radiation treatment.[22] Furthermore, other investigators have suggested a radiation-induced vascular damage when tumors are subjected to doses higher than 10 Gy;[41,42] although a very interesting theory, the latter warrants further studies on the subject.

Rao *et al*. reported encouraging results involving acid sphingomyelinase pathways when delivering doses above 8 Gy, subsequently leading to a series of local phenomena such as the activation of tumor endothelial cell apoptosis, disruption of tumor vasculature, and increase in tumor cell death.[39] The studies of Kissick *et al*. (2013) suggested that oxygen response from the first delivered dose is likely to have a major impact on the effectiveness of the second dose; the group indicated that dose modulation in relation to oxygen dynamics could result in the development of highly effective patient-specific adaptive radiotherapy.[25] The same group concluded that optimizing the timing between doses (possibly short time-settings between doses) could carry important clinical implications in the context of high dose hypofractionated treatments. In this particular context, the inclusion of complementary high performance imaging able to trace and map tumor oxygenation such as positron emission tomography used with nitroimidazole tracers and electron paramagnetic resonance oximetry may be a strategic necessity in terms of optimizing radiosurgical schedules such as RRR.[25]

Future strategies: RRR and the role of "immuno-radiosurgery" in anti-cancer treatment

Despite the positive impact of local radiation treatments in terms of local tumor control and survival in general, the mortality rate secondary to overall, whole-body metastatic activity remains an issue. In the same context, RRR may provide an efficient local surgical solution in acute/subacute settings but may not be enough to divert disease progression in the long term, particularly as a monotherapeutic/nonsynergistic approach. However, in the quest for extending the ablative effects of local radiation to distant/peripheral sites, understanding the "bio-mechanical" impact of radiation on immunodynamics remains crucial. In general, the degree and the type of cell death in a tissue-specific fashion is dependent upon variables related to dose and fractionation.[10,39,47] Modification of these radiation delivery variables leads to different levels of inflammatory changes and, subsequently, to a particular form of radiation-induced cell death called immunogenic cell death (ICD).[16] This particular process involves (among others) the modulation of calreticulin to the cell surface and the release of high-mobility group protein B1 (HMG-B1) which will ultimately enhance antigen presentation and cytokine production.[10] Moreover, ionizing radiation promotes other immune stimulatory processes such as the augmentation of major histocompatibility complex class 1 (MHC-I) expression, increased antigen presention of immunogenic epitopes, most likely (mutant) neoepitopes and subsequent expansion of tumor-reactive and pro-inflammatory CD8+ T-cells.[10,14,49] Radiation-induced activation and trafficking of antitumor effector cells might result in local and even distant (abscopal) antitumor responses.[14,24] The efficiency of the latter processes remains nonetheless subordinated to the T cells' capability to (i) penetrate and settle in the tumor tissues through vessel extravasation and tumor microenvironment infiltration, (ii) maintain solid effector properties, and (iii) enable successful T-cell target interaction(s), not disturbed by immune-supressive factors. Unfortunately, in many tumors, hindrances frequently arise at each of these levels, limiting the effects of radiation-induced immunization.[14] Despite the latter, the stimulatory effects of ionizing radiation on the immune system must indeed be considered. Preclinical studies in breast cancer models of the Demaria lab have demonstrated a clear induction of anti-tumor T-cell immunity when combining cytotoxic T-lymphocyte associated protein 4 (CTLA-4) blockade with local fractionated radiotherapy;[14] of the three tested regimens, the 8 Gy × 3 schedule proved to be the most effective enhancement, followed by 6 Gy × 5 (intermediary response) and 20 Gy × 1 (negligible response).[14] Interestingly, the same group reported similar results in mouse colon carcinoma models.[14] Although still limited to a subset of patients, monoclonal antibodies are currently being used to inhibit CTLA-4 and PD-1 (programmed cell death protein 1)–modulated immune suppressive action in metastatic non–small cell lung cancer, melanoma, and renal cancer with promising results in terms of clinical response and survival.[14,24] In view of the mounting evidence gathered over the last few years, the future management of overall metastatic activity might therefore include a combined approach of locally aggressive, ablative radiation schedules such as RRR plus T-cell-based immunotherapy, including adoptive T-cell transfer, dendritic cell vaccines, and immune checkpoint blockade.[14,24,32,47] For the above T-cell dependent treatments, the common denominator for tumor micro-environment disruption and subsequent therapeutic fulfillment hinges on the effective trafficking of anti-tumor directed immune effector CD8+ or CD4+ T-cells to cancer cells via the microvasculature.[31,34] In this very particular setting, a chemotactic cytokine (chemokine) receptor expressed on circulating tumor-reactive T cells called CXCR3 (CXC chemokine receptor 3) has been identified to be the master-regulator of intravascular cytotoxic CD8C T-cell trafficking by engaging the cognate chemokine ligand CXCL9/10 present on vessel walls. This particular receptor-ligand engagement results in stable intravascular adhesive conditions and further T-cell migration to the intratumoral space. Adjunctive therapies such as radiation and chemotherapy are even believed to be able to increase CXCL10 availability, subsequently boosting CXCR3-activity.[34] Human and murine cytotoxic CD8 T cells are also armed with two other functional chemokine receptors known as CCR2 and CRR5; these receptors are important for T-cell extravasation and, together with CXCR3, are thought to regulate specific intratumoral

T-cell activity such as retention, proliferation, and T-cell survival subsequently leading to tumor apoptosis.[34] Finally, as in other areas in the field of oncology, the identification of mathematical models able to correlate and measure distinct qualitative/quantitative immune responses to "customize" specific ablative radiation schedules remains essential in terms of the clinical outcome. The subject remains defiant yet far from inconsequential as it may lead to "made-to-measure," personalized treatments in accordance with intra- and extracranial requirements. Radiosurgical treatments structured on simple volumetric estimates with the sole purpose of providing local responses may soon be history.

CONCLUSIONS

In this study, adaptive hypofractionated gamma knife radiosurgery in selected acute/subacute settings (RRR) proved effective in terms of prompt ablation and limited normal tissue toxicity during the week of treatment and 4 weeks after treatment completion (first follow-up). High performance MRI proved crucial in terms of presurgical diagnostics, treatment planning, and optimal follow-up. We found no strong correlation between RPA classes and (i) survival up to first MRI and (ii) best ablative response during treatment and at first follow-up; this might be due to the limited number of patients included and the short period of time analyzed for the purpose of this study. However, despite the above, we believe intrinsic radiobiological factors such as tumor radiosensitivity and reoxygenation might have played a determinant role in RRR-outcome. Further studies on the subject are required. The potential impact of hypofractionation on crucial immune responses, particularly at vascular checkpoints, is worth developing in the context of RRR-treatments and also warrants further prospective studies. A second complementary paper analyzing the long-term outcome of RRR is being conceptualized; data including; data including local tumor control, ARE-development, overall survival, and clinical status from first to last follow-up will be provided and discussed.

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Conflicts of interest

There are no conflicts of interest.

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