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Research Article

A Methionine PET Targeting for Gamma Knife Radiosurgery used to Treat Recurrent Malignant Gliomas at Inoperable Stage

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Abstract

Purpose: The current study investigates the usefulness of metabolic positron emission tomography (PET) imaging (in particular with 11C-methionine (MET)), for target definition during gamma knife radiosurgery (GKRS) of locally multirecurrent malignant glioma at inoperable stage.

Patients and Methods: We retrospectively evaluated the results of GKRS with MET-PET targeting for 24 adult focally recurrent inoperable malignant gliomas treated at the Erasme Gamma Knife Center between 2007 and 2018. We evaluated the type of tumour progression (local vs remote), progression-free survival (PFS), overall survival (OS) and toxicity after MET-PET targeting of GKRS for these 24 patients.

Results: The median PFS after GKRS for the 24 patients with malignant gliomas was 5.5 (2-46) months and 4.5 (3-10), 4.5 (2-8) and 13.5 (2-46) months for glioblastoma, anaplastic glioma and grade II glioma patients, respectively. The median OS from the GKRS procedure for patients with recurrent glioblastomas (n=12) was 18 (6-45) months, 8 (6-184) months for anaplastic gliomas (n=6), and 22 (16-65) months for grade II gliomas (n=6). All patients with grade III and II multirecurrent gliomas (n=12) showed an early favourable local metabolic response, while this response was observed only in 6/12 of the glioblastomas. However, the majority (9/12=75%) of these grade II/III glioma patients further developed new lesions. GKRS treatment was associated with diverse chemotherapies in more than 50% (13/24) of cases. Post-GKRS radio-necrosis was observed in only one patient.

Conclusion: Based on a limited series of 24 patients, our study shows, for the first time, the GKRS-induced metabolic response in focally recurrent inoperable malignant gliomas. GKRS could be part of the multidisciplinary approach for multirecurrent malignant gliomas that cannot be anymore treated by surgery.

Keywords: Gamma knife radiosurgery; Gliomas; Methionine PET; Recurrence; Inoperable

1. Introduction

Malignant gliomas are infiltrating tumours, which makes complete surgical resection elusive, and tumour recurrence is more than frequent. Glioma recurrence around the resection cavity occurs in almost all patients, and the management options for evolutive malignant gliomas are limited despite advances in surgical, chemotherapeutic and radiotherapeutic techniques [1]. Moreover, the remaining glioma cells that migrate after debulking are resistant to conventional treatments [2]. Stereotactic radiosurgery (SRS), including gamma knife radiosurgery (GKRS), is often beneficial, resulting in improved survival for patients [3-10]. Nevertheless, SRS remains underutilized as part of the multimodality management of recurrent malignant gliomas [3-10]. SRS treatments can be refined with the use of various imaging approaches to improve tumour targeting. Among the different approaches, metabolic imaging using positron emission tomography (PET) in addition to conventional magnetic resonance imaging (MRI) can provide relevant information on tumour metabolism, which allows for more accurate diagnoses and treatments [11, 12]. Radiolabelled amino acids have been used in neuro-oncological practice since 1983 [13]. The largest experience with this class of PET tracers for brain tumour imaging has been gained with 11C-methionine (MET), and MET is an essential amino acid labelled with the positron-emitting isotope carbon-11, which is associated with a 20-min half-life [14, 15]. The value of PET imaging with MET (MET-PET) has been evaluated in glioma patients in terms of tumour delineation [16, 17], prognostication, histological grade and molecular IDH1 mutation [18, 19], differentiation of tumour recurrence from radiation injury [20-22], response assessment to alkylating agents [23-25] and target definition in radiotherapy planning [26-30], including re-irradiation [31]. Our group has shown for example that the addition of MET-PET data for the resection guidance of anaplastic gliomas and glioblastomas provides a target contour substantially different from that obtained by contrast-enhanced MRI alone in approximately 80% of cases and that a complete resection of the tumour area with increased methionine uptake resulted in significantly longer survival of patients [32, 33].

Gamma knife radiosurgery (GKRS) has the highest requirements in terms of imaging accuracy, as the

treatment is applied in a single high-dose session with no spatial control other than medical imaging. However, discrepancies between lesion distributions on MET-PET and magnetic resonance imaging (MRI) in patients with malignant gliomas have been evident for more than 15 years [34]. Miwa et al. [34] demonstrated that biologic imaging helps to detect tumour infiltration in brain areas with a non-specific MRI appearance in a significant number of patients. In the current study, we retrospectively evaluated GKRS, with the inclusion of a MET-PET target, as a treatment option after standard therapies for adult multirecurrent inoperable malignant gliomas. This study also aims to assess the level and timing of the MET-PET response after GKRS, local and distant tumour progression, progression-free survival, overall survival from the GKRS procedure and toxicity. GKRS was performed as part of the multimodality management of patients with recurring malignant gliomas at inoperable stage and was combined with other therapies.

2. Patients and Methods

2.1 Patients

All patients included since 2000 in the glioma database of our Gamma Knife Unit (Erasme Hospital/Brussels, Belgium) were retrospectively reviewed. All patients underwent standard multimodal treatments: surgery(-ies), radio- and/or chemotherapies, including the Stupp temozolomide-based protocol for glioblastomas [35] (Table 1). Radiosurgery treatment was planned on a Leksell GammaPlan platform to which MRI and MET-PET data files were imported. T1, T2, FLAIR, and T1 with contrast MRI sequences were acquired on Philips, ACSNT1.5, Intera 1.5 and Achieva 15 scans, and PET data were acquired on Philips. Images were collected 20 minutes after the injection of 555 MBq of MET. For treatment planning, all areas with either contrast enhancement on T1 or increased MET uptake within an area of increased FLAIR signals were considered targets. On MET-PET images, lesions were visually delineated using colour thresholding derived from a previous study [36].

Patients who were lost to follow-up or who had missing data were excluded from the study. This study was approved by the local ethics committee review board (P2019/199) of the Erasme Hospital. Since 2000, 72 adult patients (age 25-64) with malignant gliomas have been treated in our unit by GKRS using PET data. Our series included 50 grade IV glioblastomas, 12 grade III anaplastic gliomas and 10 grade II gliomas. We excluded 38 glioblastomas from this series for the following reasons: 22 patients did not receive the Stupp protocol after surgery because they underwent surgery before 2005; 14 patients had incomplete clinical follow-up; one patient was targeted by means of FDG-PET instead of MET-PET, and the remaining patient was treated with GKRS as a boost during radiotherapy. Six patients with anaplastic gliomas and 4 patients with grade II gliomas were also excluded from our final analysis because of missing metabolic data. Our final study group thus includes 24 adult patients with recurrent malignant gliomas, including 12 glioblastomas, 6 anaplastic gliomas and 6 grade II gliomas. These patients were all treated between May 2007 and September 2018.

For each patient, the following data were collected: sex; age at diagnosis; previous treatment including surgical procedures, radiotherapy and chemotherapies; functional status prior to GKRS (assessed using the Karnofsky Performance Status (KPS)); post-radiosurgical complications; adjuvant therapies associated with GKRS; follow-up data; time interval for the local response evaluated by MET-PET; time for the local and at-distance recurrence (progression-free

survival (PFS)); and overall survival (OS) after GKRS. The molecular characteristics of the gliomas included only the status of the 1p19q co-deletion. Other molecular characteristics (isocitrate dehydrogenase status and O(6) methylguanine methyltransferase methylation status) were not evaluated because data were missing for the majority of the patients.

3. Results

3.1 Demographics

The patient demographics are summarized in Table 1 and detailed in Table S1 (supplementary data). Thirteen patients (54%) received second- or third-line chemotherapy associated with GKRS (Table S1). Seven glioblastoma patients received either temozolomide (TMZ) (3), lomustine (Lom) (3) or carboplatine (Platine) (1). Three grade III glioma patients received either TMZ (2) or the combination of procarbazine, Lom and vincristine (PCV) (1), and 3 grade II glioma patients received Lom (1), TMZ (1) or PCV (1) (Table S1).

3.2 Outcome

The PFS after GKRS and the OS from the GKRS procedure are summarized in Table 2 and detailed in Table S1 (supplementary data). Of the 12 glioblastoma patients locally treated by GKRS at recurrence, 6 patients had an early unfavourable response (5 with local evolution and one at-distance of the treated area) at the first MET-PET follow-up (3 months), 6 patients had a long-term metabolic response for >= 6 months, 4 patients developed local evolution of the disease and 2 patients developed multiple new distant lesions after 6 months (Table S1). Figures 1 and 2 illustrate the representative GKRS treatment plan and the metabolic follow-up for the glioblastoma patients. All 6 grade III GKRS-treated gliomas showed a local, early metabolic response by MET-PET (between 2 and 4 months), but all 6 had developed either new lesions at the first follow-up (2-5 mo) (N=4) or local recurrence at the second follow-up (6-8 mo) (N=2) (Tables 2 and S1 for details). All 6 grade II GKRS-treated gliomas showed a local, early metabolic response by MET-PET (at 2 to 6 months posttreatment). Two patients showed remote, early (2-4 mo) new lesions (patients 20 and 23 in Table S1) without local recurrence. Systemic treatment was indicated, and the prognosis was good (OS 33 and 25). Two patients showed stable disease for more than 1 year without treatment (patients 21 and 22). Two patients showed stable disease for more than 1 year with chemotherapy associated with GKRS (patients 19 and 24 in Table S1). Only one patient with local recurrence after a response of more than one year was treated by surgery (patient 22). Two patients with pluri-focal evolution were treated by radiotherapy. One patient that had been previously irradiated on the operative field developed radio-necrosis 7 months after GKRS treatment (patient 23). Figure 3 illustrates a patient with a long-term metabolic response.

Post-GKRS radio-necrosis was observed in only one patient (patient number 23 in Table S1) with a history of previous external brain radiotherapy at a dose of 50.4 Gy for an oligodendroglioma grade II 5 years earlier. Radiologically, the patient presented with cerebral oedema 7 months after GKRS (20 Gy), and radio-necrosis was confirmed by histological analysis. Salvage palliative surgery was performed after GKRS in 6 cases (2 glioblastomas, 1 grade III and 3 grade II gliomas) in 5 patients due to local progression on MRI (using the RANO criteria) confirmed by metabolic PET-MET; imaging signs were associated with neurological symptoms (focal neurological deficit or seizures) in 2 patients and with symptomatic radio-necrosis in one patient.

	All gliomas	Grade IV gliomas	Grade III gliomas	Grade II gliomas
Number of patients	24	12	6	6
Sex	10 M (42%); 14 F (58%)	9 M (75%); 3 F (25%)	3 M (50%); 3 F (50%)	4 M (67%); 2 F (33%)
Median Age (years)	49.5 (extremes 25-64)	53 (extremes 36-64)	42.5 (extremes 37-57)	45.5 (extremes 25-63)
Histological characteristics	-	10 primary IV 2 IV2	4 OIII 2 AIII	3 OII 3 AII
conventional RT before GKRS	21	All 12	All 6	3
Median KPS before GKRS	70 (extremes 60-100)	75 (extremes 60-100)	70 (extremes 60-90)	75 (extremes 70-100)
Average time from histological diagnosis to GKRS (mo)	58 (extremes 0-252)	19.5 (extremes 5-170)	46 (extremes 0-252)	125 (extremes 96-208)
Median GKRS dose (Gy)	15 (extremes 15-24)	16 (extremes 15-20)	15 (extremes 15-20)	18 (extremes 15-24)
Median GKRS targeted volume (mm^3)	6517 (extremes 587-28383)	5565,5 (extremes 2932-18193)	7967 (extremes 1013-28383)	4394,5 (extremes 587-9228)

Abbreviations: AIII: anaplastic astrocytoma; AII: astrocytoma; F: female; GKRS: gamma knife radiosurgery; KPS: Karnofsky Performance Status; M: male; mo: months; OIII: anaplastic oligodendroglioma; OII: oligodendroglioma; RT: radiotherapy; IV: glioblastoma; IV2: secondary glioblastoma

Table 1: Patient demographics.

	Grade IV gliomas (n=12)	Grade III gliomas (n=6)	Grade II gliomas (n=6)
Median PFS (mo)	4.5 (extremes 3-10)	4.5 (extremes 2-8)	13.5 (extremes 2-46)
Median OS (mo)	17.5 (extremes 6-45)	8 (extremes 6-184)	21.5 (extremes 16-65)
Early local metabolic response	6/12 (3 mo)	All 6/6 (2-4 mo)	All 6/6 (2-6 mo)
Long term metabolic response	6/12 (6 mo)	0 (6-8 mo)	4 (> 12 mo)

Abbreviations: GKRS: gamma knife radiosurgery; mo: months; OS: overall survival; PFS: progression free survival

Table 2: Outcome.

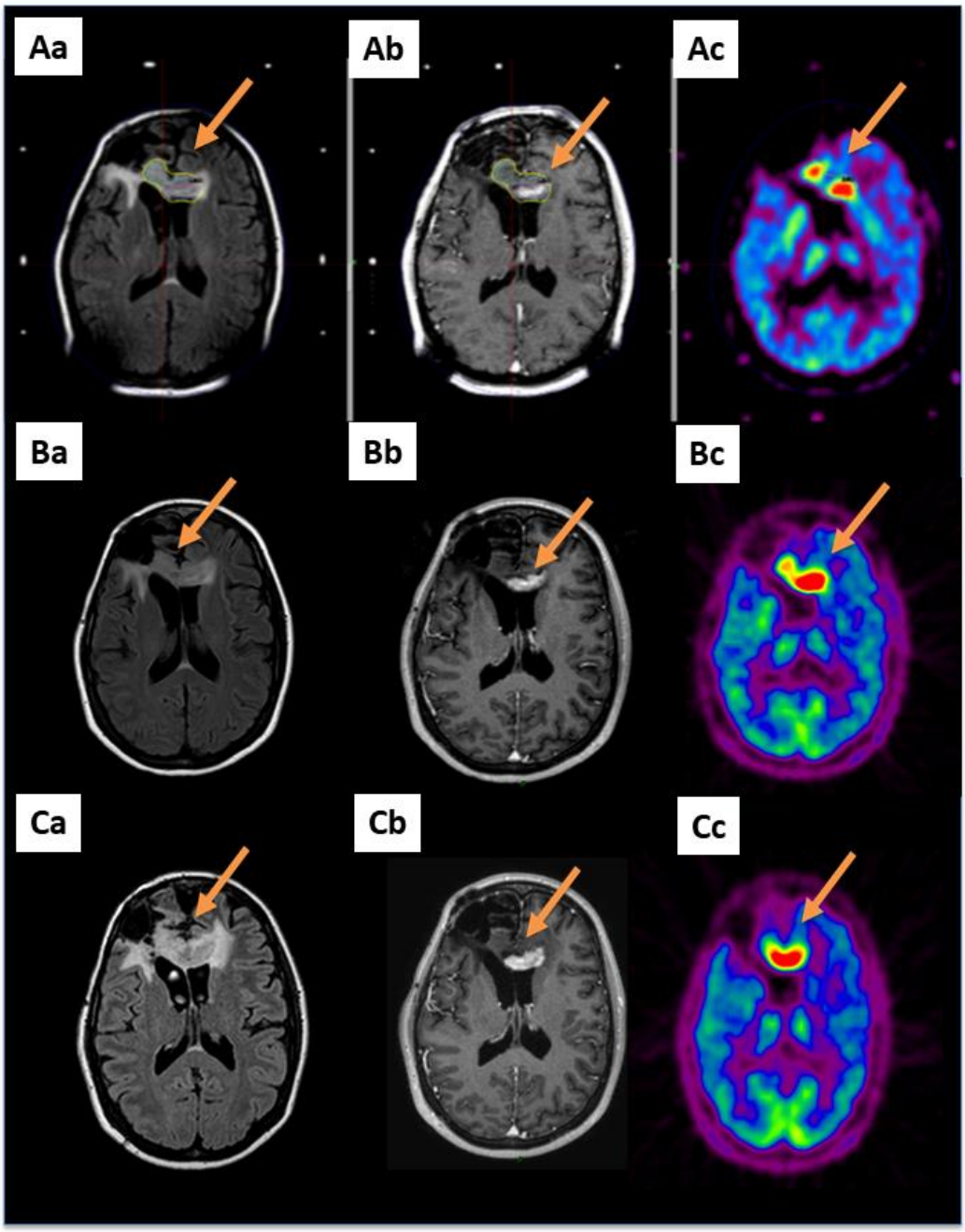

Figure 1: A 36-year-old patient with a glioblastoma (patient 6 in Table S1) already treated by the Stupp protocol after a cerebral biopsy presented with a radiological progression located in the corpus callosum 2 years after her diagnosis (arrows). A GKRS treatment, 15 Gy on a volume of 9716 mm^3 including the MET-PET target, was performed. Aa: MRI reformatted axial FLAIR; Ab: reformatted axial T1-weighted with contrast and Ac: MET-PET study performed on the day of the GKRS treatment; B and C show the same sequences 3 and 6 months after GKRS, respectively. Three months after GKRS, MET-PET (Bc) indicated suspected local failure. Six months after the GKRS treatment, all exams confirmed the progression (C: same sequences).

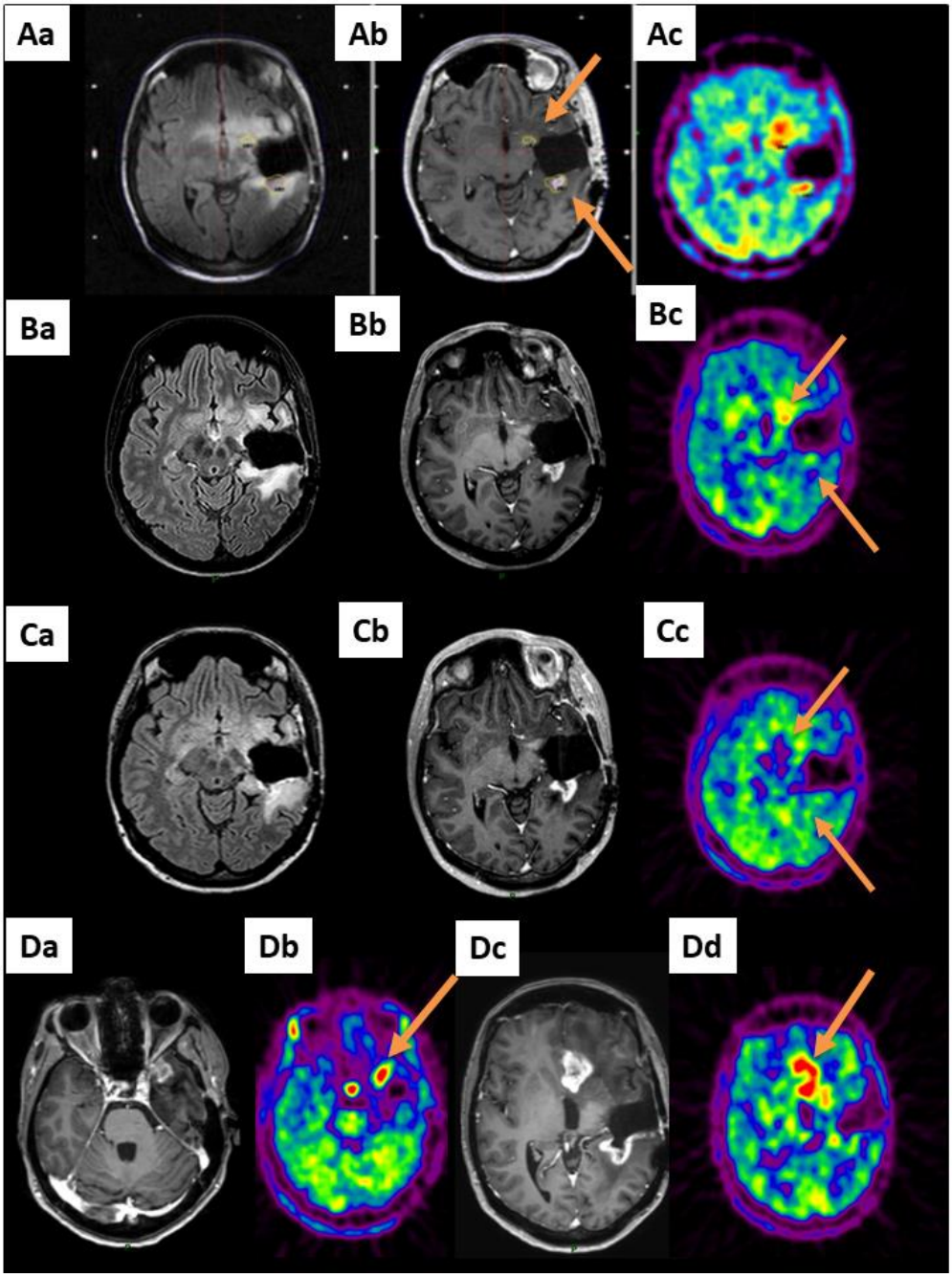

Figure 2: A 42-year-old patient (patient 7 in Table S1) already treated by the Stupp protocol for left temporal glioblastoma after large surgery presented with a radiological progression located in the operative cavity wall 6 months after her diagnosis (2 spots, arrows). A GKRS treatment, 15 Gy covering a total volume of 2932 mm^3 including the 2 MET-PET targets, was performed. Aa: MRI reformatted axial FLAIR, Ab: reformatted axial T1-weighted with contrast and Ac: MET-PET study on the day of the GKRS treatment (2 targets, arrows). B and C show the same sequences 3 and 6 months after GKRS, respectively. Three months (B) and 6 months (C) after GKRS, the metabolic exams revealed a local response. However, six months after the treatment, the MRI and MET PET exams revealed remote progression (Da and Dc: axial T1-weighted with contrast and Db and Dd: MET-PET).

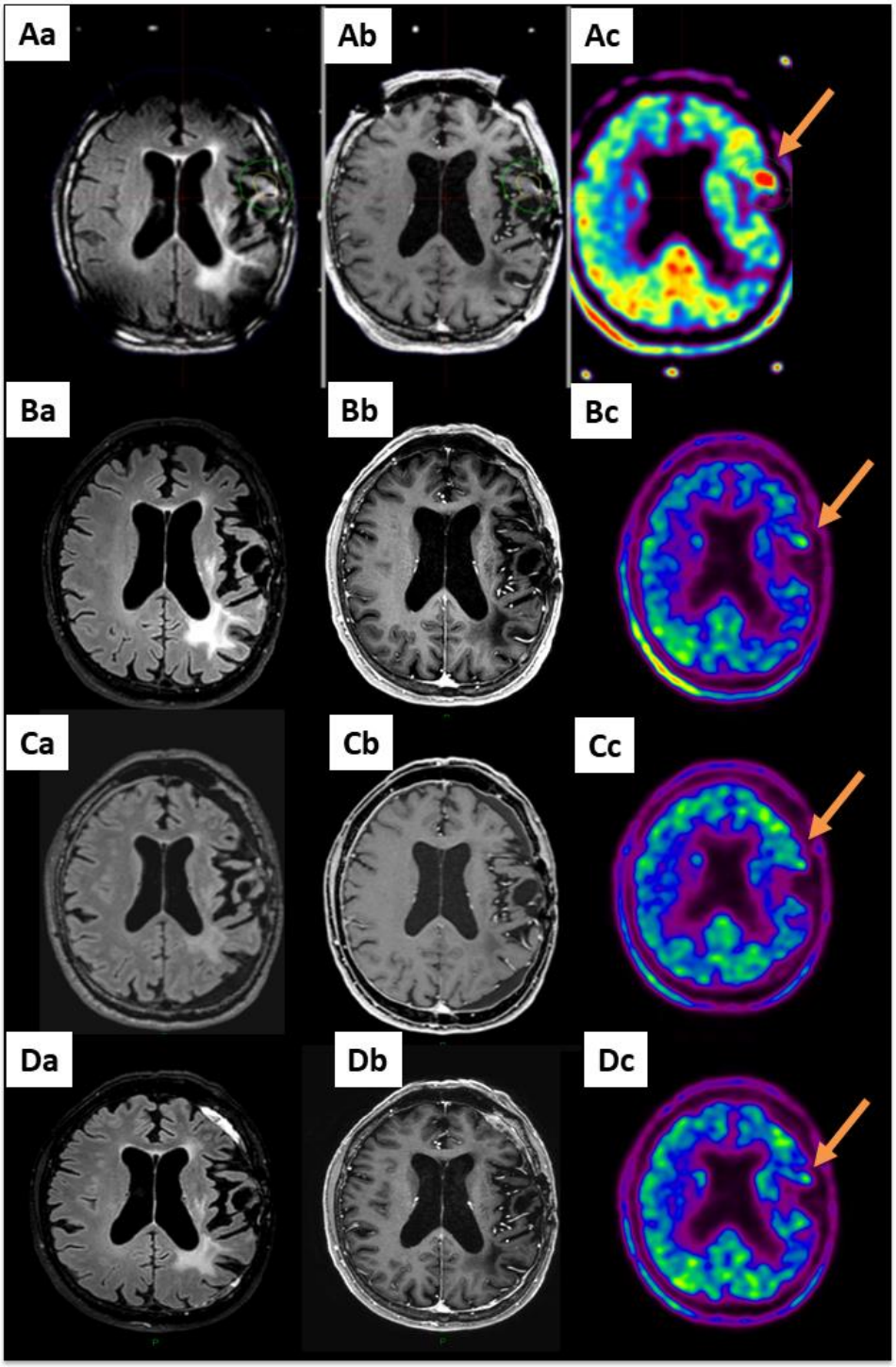

Figure 3: A 63-year-old patient with a grade II evolutive astrocytoma (AII) (patient 19 in Table S1) already treated by PCV chemotherapy, radiotherapy and TMZ chemotherapy after large surgical resection received GKRS treatment 20 Gy on a volume of 2312 mm^3 including the MET-PET target (arrow). Aa: MRI reformatted axial FLAIR, Ab: reformatted axial T1-weighted with contrast and Ac: MET-PET study performed on the day of the GKRS treatment. B, C and D show the same sequences 3, 6 and 12 months after GKRS: long-term local response.

4. Discussion

The management of multirecurrent malignant gliomas is challenging due to their spatial and temporal heterogeneity, ability to infiltrate the surrounding brain tissue and interaction with the tumour microenvironment [37, 38]. Numerous recent clinical trials using second-line chemotherapy [39, 40] or immunotherapy [41, 42] have failed to improve survival. The efficacy of GKRS at recurrence can also be of limited efficacy mainly due to the highly infiltrative nature of the gliomas. GKRS limited efficacy can also be linked to the difficult interpretation of the morphological changes demonstrated on classical neuroimaging after primary treatment of gliomas, leading to a high level of incertitude in the definition of recurrent lesions as targets for GKRS treatment. The discrepancy between lesion distributions on MET-PET and MRI in patients with malignant gliomas has been stressed in the literature [34] and is well demonstrated in a preliminary account of our experience with MET-PET integration in GKRS planning [43]. A study on 79 glioblastoma patients revealed that the metabolically active tumour volume on metabolic images prior to histological diagnosis is considerably larger than the volume of contrast enhancement (median volumes 23.8 ml versus 13.5 ml) [44]. We therefore took the option to integrate metabolic images by means of MET-PET to the GKRS planning of multirecurrent inoperable malignant gliomas and to follow the metabolic response after treatment. Such integration has already been proven useful for classical or conformal radiation therapy and carbon ion therapy of gliomas [26, 28, 30, 31, 45]. To the best of our knowledge, this is the first study evaluating the metabolic response of GKRS for recurrent grade II and III gliomas.

In our current retrospective study based on 24 adult multirecurrent malignant glioma patients, we observed that all patients with grades III and II recurrent gliomas demonstrated an early favourable local metabolic response to GKRS, while this outcome was only the case for 50% of the glioblastoma patients (Table 2). However, due to the infiltrative nature of these tumours, the majority (75%) of these grade II and III glioma patients developed new lesions. Several recent publications have studied the indication, efficacy and radio-necrosis risk of GKRS for recurrent grade IV glioblastomas [3-7, 46-49]. In our small series we observed only one case of radio-necrosis in a grade II glioma after previous external brain radiotherapy.

In our study including 12 recurrent glioblastomas, we observed that half of them demonstrated long-term metabolic control for more than 6 months. However, the other half presented early evolution after 3 months with either local failure or distant lesions. The median PFS for this glioblastoma population is 4.5 months. In the study by Frischer et al. on 42 recurrent glioblastomas, the time to radiological progression after GKRS was 4.4 months and mainly occurred beyond the GKRS-irradiated area [6]. In our series, the marginal dose was always equal to or greater than 15 Gy. In the retrospective large study of Niranjan et al. on 297 patients with recurrent or residual glioblastomas treated by GKRS, the important prognostic variables included tumour volume <14 cm3, marginal radiation dose of >= 15 Gy and younger age (<60 years) of the patients [3]. In this series, adverse radiation effects were noted in 23% of cases and were mainly controlled with corticosteroids [3]. The study by Imber et al. (2017) on 174 recurrent glioblastomas also confirmed that young age, small recurrence, and high prescription dose were prognostic variables for a lower risk of symptomatic secondary effects [7]. It was recently shown in a small cohort of 9 patients with recurrent glioblastoma that a

single dose of bevacizumab prior to GKRS permitted safe prescription dose escalation up to 22 Gy [47].

Because of the infiltrative nature of the disease, 54% of our patients received second- or thirdline chemotherapy associated with GKRS as we frequently performed after a surgery. Our series is therefore heterogeneous and it is difficult to ascertain if the limited response that we have is because of the GKRS or chemotherapy, or both. A single centre prospective phase II study is currently assessing the safety and efficacy of the addition of early stereotactic GKRS for residual tumours after surgery (and the standard treatment) of newly diagnosed glioblastoma [50]. All patients will receive GKRS with 15 Gy (prescribed to the 50% isodose enclosing all residual tumour areas) early (within 24-72 h) after surgery.

5. Conclusion

Our study aims to highlight the potential of using metabolically targeted GKRS in the multimodality management of inoperable malignant glioma local recurrence. Based on a limited series of 24 patients, the current study demonstrates the GKRS-induced metabolic response in multirecurrent malignant gliomas. Because GKRS could be part of the multidisciplinary approach for multirecurrent malignant gliomas that cannot be anymore treated by surgery, we will evaluate the actual benefits of GKRS in patients with malignant glioma local recurrence in a prospective controlled clinical trial.

Declarations

Not applicable.

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Supplementary data

Patient	Sex	Age (Y)	Glioma Grade	Previous treatments	KPS-GKRS	GKRS dose (50%)	GKRS targeted vol (mm3)	GKRS Combined treatment	PFS (mo)	OS (mo)	Type of tumour progression
1	F	60	IV	Stupp	90	15	7500	-	8	32	Local and remote at 8 mo
2	F	53	IV	Stupp/2dRes	70	17	15960	-	3	6	Local at 3 mo
3	M	45	IV	Stupp/lom	80	15	6558	Res	3	8	Remote at 3 mo
4	F	61	IV	Stupp	60	15	18193	-	10	18	Local at 10 mo
5	M	59	IV2	Bi/PCV/Res/Stupp/lom	100	15	4257	Lom	6	36	Local at 6 mo
6	F	36	IV	Stupp	100	15	9716	TMZ	3	45	Local at 3 mo
7	F	42	IV	Stupp	80	15	2932	Lom	6	13	Remote at 6 mo
8	M	64	IV	Stupp/2dRes/TMZ	70	20	4573	TMZ	3	32	Local at 3 mo
9	F	53	IV2	Stupp/2dRes/TMZ/lom	70	20	3867	Lom	8	13	Local at 8 mo
10	F	46	IV	Stupp	70	20	14955	-	3	36	Local at 3 mo
11	F	51	IV	Stupp	70	18	4251	TMZ	3	17	Local at 3 mo
12	F	54	IV	Stupp/2dRes/TMZ/lom	80	20	3750	Platine	7	Alive (9)	Local at 7 mo
13	F	52	OIII	Res/RT/TMZ/PCV	90	15	7901	PCV	6	7	Local at 6 mo
14	M	42	OIII	Res/RT	70	15	1013	-	2	27	Remote at 2 mo
15	M	37	OIII	Res/RT/TMZ	70	15	28383	-	8	Alive (184)	Local at 8 mo
16	M	57	OIII	Res/RT/TMZ/PCV	70	15	8033	-	3	6	Remote at 3 mo
17	F	38	AIII	Res/RT/2dRes/ 3rdRes/TMZ	70	20	1438	TMZ	4	Alive (9)	Remote at 4 mo

18	F	43	AIII	Res/RT/TMZ	60	15	17480	TMZ	5	6	Remote at 5 mo
19	M	63	AII	Res/2dRes/PCV/ RT/TMZ	80	20	2312	Lom	16	Alive (16)	Local and remote at 16mo
20	M	58	AII	Res/2dRes/TMZ/PCV	70	15	6923	PCV	2	33	Remote at 2 mo
21	M	48	AII	Res/2dRes	70	15	587	-	46	65	Remote at 46 mo
22	F	25	OII	Res	70	24	625	-	15	17	Local at 15 mo
23	M	43	OII	Res/2dRes/3rdRes/TMZ/ 4rRes/RT	100	20	6477	-	4	Alive (25)	Remote at 4 mo
24	F	30	OII	Res/2dRes/TMZ/ 3rdRes/RT	90	16	9228	TMZ	12	Alive (18)	Remote at 12 mo

Abbreviations: AIII: anaplastic astrocytoma; AII: astrocytoma; Bi: biopsy; F: female; GKRS: gamma knife radiosurgery; KPS: Karnofsky Performance Status; lom: lomustine; M: male; mo: months; OIII: anaplastic oligodendroglioma; OII: oligodendroglioma; OS: overall survival; PCV: procarbazine lomustine vincristine; PFS: progression free survival; Res: surgical resection; RT: radiotherapy; TMZ: temozolomide; IV: glioblastoma; IV2: secondary glioblastoma

Table S1: Patient demographics.