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Re-Irradiation for Recurrent Brain Tumors: A Retrospective Study from a Tertiary Hospital in Saudi Arabia

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Abstract

Objective: To analyze the post-re-RT progression-free survival (PFS) and incidence of radio-necrosis (BRN) in patients with recurrent primary brain tumors and to explore the associated factors.

Method: A retrospective cohort study that included 15 pediatric and adult patients with primary brain tumors who were treated with re-RT between 2011 and 2020. The study endpoints included the post-re-RT PFS, which were analyzed using Kaplan-Meier survival analysis, and the incidence of radio-necrosis. Baseline demographic and clinical data, primary radiation therapy (RT1) parameters and outcomes, and re-RT parameters and outcomes, were analyzed as factors for the two outcomes.

Result: Of the 15 participants, 7 had glioblastoma and 5 had anaplastic ependymoma. The mean interval from first RT to re-RT was 24 months (range=2-60 months). The mean total cumulative dose after re-RT as per EQD2 (equivalent dose in 2 Gy) fractions was 101.97 Gy (max 135.6 Gy). The total mean (max) cumulative doses for organs at risk as per EQD2 after re-RT were 54.05 (92.93) Gy for brain stem, 41.19 (87.94) Gy for optic chiasma, and 28.79 (77.18) Gy and 28.6 (88.71) Gy for left and right optic nerves respectively. Disease progression occurred in 10/15 patients, and the median PFS was 4 months (95%CI=0-9.1). Although not statistically significant, PFS was likely to be prolonged in case of low-grade tumors, longer RT1-re-RT time. Radiation necrosis occurred in 2 patients.

Conclusion: The expected clinical benefits against the adverse effects should be contemplated for re-irradiation in primary brain tumors.

Keywords: Re-irradiation • Primary brain tumor • Glioblastoma • Glioma

Introduction

Primary brain tumors constitute a heterogeneous group of benign and malignant tumors that develop in the brain structures including parenchyma and annex tissues. They are characterized by a high mortality and poor functional outcome, resulting into a substantial disease burden, and high propensity for recurrence [1-3]. The worldwide incidence of primary brain cancers was estimated as 10.82 per 100 000 person-years, with a significant age-disparity depending on the tumor type and histology [4].

Recent progress in molecular biology, imaging, surgery and radiation therapy has enabled advanced understanding and management of primary brain tumors, especially gliomas and primary central nervous system lymphomas that represent the most common pathological types. Nevertheless, the standard treatment remains relatively aggressive, including surgical resection followed by adjuvant radiotherapy (RT), using either conformal intensity-modulated radiation therapy (IMRT) or stereotactic radiotherapy (SRS), and in some cases adjuvant chemotherapy (CT) [3,5-8]. Furthermore, in refractory or relapsing cases a re-irradiation (re-RT) and or re-resection can be proposed, entailing concerns regarding the risk of radio-necrosis that may occur several months to several years following re-RT [9-13].

Currently, there is no standard of care, notably dose regimens, regarding re-RT of brain tumors and the prospective data addressing this approach are scarce [9]. The safety of re-RT approach is limited by the capacity of brain recovery after radiation, which depends on the initial biologically effective dose (BED) as well as on the time interval between the primary radiation (RT1) and re-RT (RT1-re-RT interval) [11]. Consequently, a low RT1 dose and an increased RT1-re-RT interval are supposedly favorable for a re-RT indication [11]. However, some data have shown no correlation between RT1-re-RT interval and brain tolerance to re-RT [9,10]. On the other hand, recent advances in RT technique, such as IMRT and SRS, allowed reduction of the treatment volume, thereby sparing normal tissue and reducing the proportional risk of radiation toxicity [9,10,14].

In our center, which is a referral center in radiation oncology, a selected number of patients with recurrent primary brain tumor have benefitted from re-RT over the last years. This study aims at analyzing the safety and efficacy of re-RT among this cohort of patients, by estimating the incidence risk of brain radio-necrosis (BRN) and the progression-free survival (PFS), post re-RT, and analyzing the associated treatment parameters, notably the cumulative radiation doses for brain and organs at risk. Such data would provide a more nuanced insight into the clinical benefit of re-RT for brain tumors and enable determine eventual irradiation dose thresholds and toxicity profiles, which may give direction for future randomized trials. Additionally, data from this study would supply further systematic reviews and meta-analyses.

Methods

Design and setting

A retrospective cohort study was conducted at the Radiotherapy Unit of Oncolcogy in King Faisal Specialist Hospital and Research Centre, Jeddah, between 2011 and 2020. The study received ethical approval of the institutional review board of Jeddah.

Participants

Fifteen patients were identified with primary brain tumors that were treated with re-RT during the study period, either with 3-D conformal radiotherapy,

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IMRT or SRS. Both pediatric and adult patients were included.

Data collection

A pre-formatted Excel sheet was used to collect the following data: (1) baseline demographic and clinical data including age, gender, pathology type, grade, and side; (2) RT1 parameters including radiation technique, total radiation dose, dose per fraction, number of fractions, duration, and maximal dose for optic nerves, optic chiasm and brainstem; (3) RT1 outcomes including time from RT1 to disease progression and re-resection; (4) re-RT parameters including RT1-re-RT interval, technique, total radiation dose, dose per fraction, number of fractions, duration, and maximal dose for optic nerves, optic chiasm and brainstem, in addition to the cumulative radiation doses for the same structures; (5) re-RT outcomes including progression and time from end of re-RT to progression, and BRN. Alpha beta ratio of 3 (for late responding organs) was used for re-RT composite dose calculations. Patients were assessed clinically for neuropathy in.

Statistical methods

Statistical analysis was performed with the Statistical Package for Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequency and percentage, while numerical variables are presented as mean ± standard deviation (SD) or median (range) as applicable. Kaplan-Meier survival function was used to plot the survival curve for the progression-free time after re-RT, and to estimate the mean and median PFS. Further, factors associated with PFS were analyzed using Kaplan-Meier survival with calculation of the Log-rank; aLog-rank<0.05 was considered to reject the null hypothesis.

Results

Demographics and first radiation therapy parameters

Fifteen patients with brain re-irradiation were eligible and were included in the study, age range was 11-75 years and 8 of them were male. Pathology showed 7 cases of glioblastoma and 5 cases of anaplastic ependymoma, and 13 patients were grade III or IV. The first RT used VMAT in 12 patients, the mean duration was 42 days, and the median number of fractions was 30. The median maximal equivalent dose in 2 Gy (EQD2) received to brainstem was 37.05 Gy. Disease progression occurred after a mean time of 29 months and 7/15 underwent re-resection (Table 1).

Table 1. Patients' demographics data and first radiation therapy parameters

Parameter	Category	Frequency	Percentage
Demographic and clinical data			
Age (years)	Mean, SD (range=11-75)	33.73	19.11
Gender	Male	8	53.3
	Female	7	46.7
Radiation side	Right hemisphere	9	60.0
	Left hemisphere	4	26.7
	Midline	2	13.3
Lobe	Frontal	6	40.0
	Parietal	4	26.7
	Occipital	1	6.7
	Temporal	1	6.7
	Other (central or diffuse)	3	20.0
Pathology	Glioblastoma	7	46.7
	Anaplastic Ependymoma	5	33.3
	Astrocytoma	1	6.7
	Ependymoma	1	6.7
	Meningeal melanomatous	1	6.7
Grade	Grade II	1	6.7
	Grade III	6	40.0
	Grade IV	7	46.7
	Missing	1	6.7
Treatment parameters			
Radiation technique	3-D	3	20.0
	VMAT	12	80.0
Total Radiation dose (Gy) / Fractions	35/10#	1	6.7
	54/30#	1	6.7
	56/28#	1	6.7
	59.4/33#	4	26.7
	60/30#	8	53.3
Dose per fraction (Gy)	1.8	6	40.0
	2	8	53.3
	3.5	1	6.7
No. fractions	Median, range	30	10, 33
Radiation therapy duration (days)	Mean, SD	42	11.13
	Median, range	42	11-64
Maximal dose (Gy)			

Left optic nerve	Median, range	10.6	0.4 - 51.8
Right optic nerve	Median, range	7.0	0.4 - 54.7
Optic chiasm	Median, range	37.6	0.6 - 55.8
Brainstem	Median, range	50.6	1.0 - 57.6
Outcomes			
Time from end of radiation to progression (months)	Mean, SD	29.0	15.11
	Median, range	30.0	11 - 47
Re-resection	No	8	53.3
Time from end of first radiation to re-resection (months)	Median, range	30.0	11 - 56
Values are frequency and percentage, except where otherwise specified.			

Re-irradiation parameters

The mean interval from first RT to re-RT was 24 months (range=2-60). The mean total cumulative dose after re-RT as per EQD2 was 101.97 Gy (max 135.6 Gy). The total mean (max) cumulative doses for organs at risk as per EQD2 after re-RT were 54.05 (92.93) Gy for brain stem, 41.19 (87.94) Gy for optic chiasma, and 28.79 (77.18) Gy and 28.6 (88.71) Gy for left and right optic nerves respectively. The median total re-radiation dose was 35 Gy delivered over a median 10 fractions and over a mean period of 18.7 days. The brainstem received a median maximal dose EQD2 of 17 Gy, resulting in a median cumulative dose of 54.7 Gy (Table 2). No evidence of neuropathy was noted clinically.

Table 2. Re-irradiation parameters

Parameter	Category/(unit)	Mean	SD	Median	Range	N	%
Treatment parameters							
RT1–re-RT interval	(months)	24.0	16.0	20.0	2, 60		
Radiation technique	3-D					4	26.7
	VMAT					9	60.0
	SRT					2	13.3
Total radiation dose	(Gy)	32,43	13.09	35	10.00, 54.00		
Dose per fraction	(N)	4,38	4.57	3	1.80, 18.00		
No. fractions	(N)			10	1, 30		
RT duration	(days)	18.7	15.5	13.0	1.0, 50.0		
Maximal doses							
Left optic nerve	(Gy)			4.0	0.2, 38.2		
Right optic nerve	(Gy)			2.0	0.3, 37.6		
Optic chiasma	(Gy)			6.0	0.5, 36.8		
Brainstem	(Gy)			10.0	0.5, 38.0		
Cumulative doses§							
Total EQD2	(Gy)	101.97	15.68	102.75	66.00, 135.00		
Total BED	(Gy)	168.04	26.73	163.34	110.00, 226.00		
Max. left optic nerve	(Gy)	28.79	26.79	22.22	0.96, 77.18		
Max. Right optic nerve	(Gy)	28.62	29.57	18.90	1.05, 88.71		
Max. Optic chiasma	(Gy)	41.20	30.17	49.41	1.82, 87.94		
Max. Brainstem	(Gy)	54.06	32.96	60.24	2.40, 92.93		
Chemotherapy	No					9	60.0
	Yes					6	40.0
Outcomes							
Progression	No					5	33.3

	Yes					10	66.7
Time from end of RT to progression	(months)			4.5	0.0, 13.0		
Radiation necrosis	No					13	86.7
	Yes					2	13.3
RT1: First radiotherapy; re-RT: Re-irradiation; EQD2: equivalent dose in 2 Gy fractions; BED: Biologically Effective Dose.§ Cumulative radiation dose = dose for 1st radiotherapy + dose of re-irradiation							

Outcomes-Progression and radiation necrosis

Subsequent to re-RT, disease progression occurred in 10/15 patients after a median follow up time of 4.5 months (range=0-13). The mean and median PFS were 5.13 months (95%CI=2.51-7.76) and 4 months (95%CI=0-9.1) respectively (Figure 1).

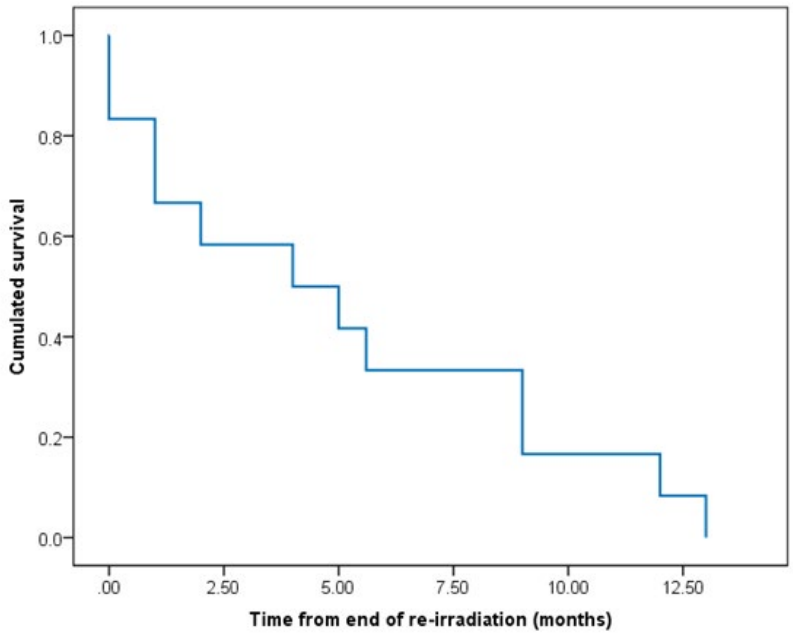

Figure 1. Progression-free survival after re-irradiation in patients with recurrent primary brain tumor. Caption: Kaplan-Meier survival curve: event=progression or death; time from end of re-irradiation to progression, death or last follow up. The curve shows a median progression-free survival of 4 months.

Radiation necrosis occurred in 2 patients, giving an incidence of 13.3% (95%CI=1.7%-40.5%) (Table 2). It was confirmed on MRI spectroscopy. The characteristics of the two patients who developed brain radiation necrosis are presented in (Table 3). Both were female, aged 11 and 46 years old. Intervals between first RT and re-RT were 20 and 12 months. Both patients had disease progression.

Table 3. Characteristics of the two radiation necrosis cases

Parameter	Case 1	Case 2
Demographic and clinical data		
Age (years)	46	11
Gender	Female	Female
Radiation side	Left	Right
Lobe	Frontal	Frontal
Pathology	Glioblastoma	Anaplastic ependymoma
Grade	IV	III
First radiotherapy parameters		
Radiation technique	VMAT	VMAT
Total Radiation dose (Gy)	60	59.4
Dose per fraction	2	1.8
No. fractions	30	33
Radiation therapy duration (days)	55	46

Maximal dose (Gy)		
Left optic nerve	2.6	42.9
Right optic nerve	2.0	53.1
Optic chiasma	4.5	53.5
Brainstem	4.7	53.8
Re-resection	Yes	No
Time to progression (months)	17	10
Re-irradiation parameters		
RT1-RE-RT interval (months)	20	12
Radiation technique	VMAT	3-D
Total Radiation dose (Gy)	27.50	30
Dose per fraction	5.5	3
No. fractions	5	10
Radiation therapy duration (days)	8	11
Maximal dose (Gy)		
Left optic nerve	0.68	30.0
Right optic nerve	0.51	30.0
Optic chiasma	0.85	30.0
Brainstem	0.85	30.0
Cumulative doses (Gy)		
Total EQD2	106.75	93.02
Total BED	177.92	155.04
Max. left optic nerve	3.28	77.18
Max. Right optic nerve	2.51	86.98
Max. Optic chiasma	5.35	87.36
Max. Brainstem	5.55	87.65
Outcome		
Progression	Yes	Yes
Death	No	Yes
PFS (months)	4	2

RT1: First radiotherapy; re-RT: Re-irradiation; PFS: progression-free survival; EQD2: equivalent dose in 2 Gy fractions; BED: Biologically Effective Dose.

Factors associated with progression-free survival

The Kaplan-Meier survival analysis showed no statistically significant factor associated with PFS (Log-rank>0.05); however, some observations are worth noting. PFS was relatively longer among patients with grade II disease (9.0 vs <6 months). Regarding treatment parameters, a longer PFS was associated with a longer RT1-re-RT interval, longer re-RT duration. The two patients who developed brain necrosis one had glioblastoma and the

Table 4. Factors associated with progression-free survival (Kaplan-Meier survival analysis)

Parameter	Category	Mean	95%CI		Log-Rank
Demographic and clinical data					
Age (years)	≤33	5.5	1.4	9.6	
	>33	4.8	1.1	8.5	.985
Gender	Male	5.9	1.8	9.9	
	Female	4.1	1.1	7.1	.403
Radiation side	Rt hemisphere	3.3	0.5	6.2	
	Lt hemisphere	8.7	3.6	13.8	
	Midline	9.0	9.0	9.0	.220
Grade	Grade II	9.0	9.0	9.0	
	Grade III	5.8	0.2	11.3	

	Grade IV	4.0	0.1	7.9	.901
Treatment parameters					
RT1 to re-RT interval (months)	≤20	3.7	0.4	7.0	
	>20	7.1	3.1	11.1	.434
re-RT duration (days)	≤13	4.5	1.7	7.3	
	>13	7.0	0.0	14.1	.641
Cumulative total equivalent dose (Gy)	≤102	18.20	3.12	33.29	
	>102	7.03	2.10	11.96	.680
Chemotherapy	No	3.7	0.5	6.9	
	Yes	7.2	3.1	11.3	.193
Outcomes					
Radiation necrosis	No	5.6	2.5	8.7	
	Yes	3.0	1.0	5.0	.342

Kaplan-Meier survival analysis; event= progression or death after re-radiation RT1: First radiotherapy; re-RT: Re-irradiation.

other anaplastic ependymoma had a relatively shorter PFS (mean=3.0 vs 5.6 months, p=0.342) compared to their counterparts respectively (Table 4).

Discussion

Summary of findings

Over the 10-year period of the study, only 15 patients underwent re-RT for primary brain tumor in our institution. With respect of the size limitation of this cohort, findings support that recurrent or treatment-resistant, high-grade glioblastomas and anaplastic ependymomas represent the most common indications of re-RT in primary brain tumors. These tumors are characterized with early progression after the first treatment, leading to shortened intervals between the first RT and Regarding safety in our institute, findings suggest that re-RT is associated with an incidence of brain radio-necrosis of 13.3%.

Indications of brain re-irradiation

The first published data regarding re-RT of the cranium and CNS date back to nearly one century, with the works of Beclere and Levy reporting cases of single or twice re-RT [15,16]. In a historical series of 16 patients with brain tumors, mainly gliomas, published in 1926, 2 of the cohort patients were reirradiated after 6 and 12 months of the first RT respectively [17]. Relapsed brain tumors constitute the most common indication of fractioned re-RT, which remains the only treatment option in majority of these patients. Several pathological types of primary brain tumors have been reported in re-RT cohorts, notably glioblastomas, anaplastic gliomas, medulloblastomas, ependymomas and meningiomas [9,18]. In the pediatric population, recurrent medulloblastoma/primitive neuroectodermal tumors, germinoma and non-germinomatous germ cell tumors, and all-grade gliomas were reported as indications for re-RT, which is often adjunctive to re-resection [19-21]. Both in adults and children, recurrence in primary brain tumors is often observed in high-grade tumors or atypical ones [21-23]. This is consistent with the present study's cohort including 40.0% and 46.7% of grade III and IV tumors, respectively. Consequently, the primary therapeutic plan for such patients with high recurrence profile should be adapted at two levels: first, to reduce the risk of recurrence or delay its occurrence, by performing a more aggressive surgery to minimize the residual disease.

The indication of re-RT is not limited to primary brain tumors, brain metastasis was early considered among the eventual indications of brain re-RT [24]. However, unlike primary brain tumors, the metastatic indications often require whole brain radiotherapy due to the frequent presence of multiple, diffused lesions to be treated, which may result in a higher risk of brain atrophy or failure [25,26]. Nonetheless, this indication was out of the scope of the present study.

Efficacy and safety balance of brain re-irradiation

It is common knowledge that the growing use of re-RT in both primary and metastatic brain tumors is associated with improved overall survival especially with the advent of high-precision RT techniques. However, the expected clinical efficacy should be assessed cautiously and weighed against the risk of radiotoxicity on the healthy structures notably the brain parenchyma and organs at risk such as the optic chiasm and optic nerves. Such caution balance combined with the scarcity of clinical data result in lack of evidence-based consensus and persisting controversies regarding the dosimetry and treatment regimens of such patients [27,28]. Further, the growing number of single-center reports is inconsistent with respect of the efficacy and safety profiles.

Findings from the present study suggest a low-efficacy profile for re-RT given the high incidence of disease progression (66.7%) occurring early, i.e., with a median time of 4.5 months from the end of re-RT. On the other hand, the safety profile of re-RT in the present cohort was relatively high, as only 2 patients developed brain radio-necrosis representing an incidence risk of 13.3%; however, the severity of the necrotic lesions in the two concerned patients and their respective functional outcomes were not reported. Further, given the small size of the present cohort, the incidence of radio-necrosis can statistically be inferred with a large confidence interval of 1.7%-40.5%, which is conclusive regarding the safety profile.

By comparison, a retrospective cohort by Stiefel et al. analyzed the outcomes of 76 patients with recurrent brain tumors, of whom 34 (44.7%) were primary and the others metastatic tumors. Outcomes in patients with primary tumors showed a median overall survival of approximately 14 months (range=21-42 months) after re-RT, while the median time to local recurrence was not reached due to high proportion of censoring and was less than 6 months in majority of non-censored patients. Regarding radio-toxicity, authors did not carry out separate analysis for the primary tumors group; instead, they reported an overall incidence of radio-necrosis of ~12%, including 5.3% in the acute phase (<12 weeks post-re-RT). Furthermore, low-grade toxicity events such as edema, headache and fatigue, were observed in 74% of the patients [23]. A comparable incidence of radio-necrosis was in our present study; however, we did not report the low-grade toxicity events.

A clinical trial by Møller et al. randomized 31 candidates for brain re-RT for recurrent high-grade glioma, of whom 81% had glioblastoma, into 4 treatment groups, each a specific sequential regimen. Of the 4 groups, 3 had a planning target volume (PTV)<100 cm3 including Group 1 (3.5 Gyx10); Group 2 (3.5 Gyx10+7Gy boost); and Group 3 (5.9 Gyx5); whereas the 4th group (39 Gy x 10) had a PTV 100 cm3-300 cm3. The median PFS in the total study population was 2.8 months and the median overall survival was 7 months. However, due to high censoring and early mortality,

only 7 patients reached a PFS of 2.5 months, 5 of them received the first regimen (3.5 Gyx10, PTV<100 cm3) and 2 received the second one (3.5Gy x 10+7Gy boost, PTV<100 cm3). Beside these low efficacy profiles, a low-safety profile was reported including high rate of minor early toxicity and serious late events in 3 out of 7 patients with PFS>2.5 months, including radio-necrosis and irreversible white matter changes with neurofunctional sequelae [29].

In pediatric patients, a 24-year retrospective study by Bouffet et al. reported a higher efficacy profile in a series 18 children who were selected for full re-RT, with or without re-resection, among a total 47 with recurrent ependymoma. Re-irradiation was associated with a 3-year survival rate of 81%, compared with only 7% among non-re-irradiated children. Additionally, re-irradiation was associated with a significantly delayed disease progression/relapse (3-year PFS=61% vs 25%) compared to the initial relapse after the first RT respectively, p=0.003. However, this high-efficacy and survival profile was achieved at the price of a significant decline in the intellectual quotient in re-irradiated children from pre to post-re-RT times [30].

Improving efficacy and controlling radiotoxicity in re-irradiation

Although not statistically significant, due to small sample size, findings from the present study suggest the presence of factors that may improve the post-re-RT prognosis, notably by prolonging the PFS. Tumor characteristics that showed association trend with PFS included lower tumor grade having longer PFS than high-grade. PFS showed likelihood of positive association with RT1-re-RT interval and re-RT duration, and was likely to be increased in patients who received adjuvant chemotherapy.

Observations from animal and clinical studies support the relevance of these factors as determinant of both the efficacy and brain tolerance to re-RT [9]. In an interesting cohort including 233 patients with recurrent grade II (40%) and III (22%) gliomas and glioblastoma (38%), Combs et al. proposed a prognostic score to determine potential candidates for re-RT based on the prognostic value of the baseline clinical and pathological characteristics. Findings demonstrated that the tumor histological type, patient age at diagnosis, and RT1-re-RT interval were the strongest predictors of survival post re-RT [31]. The use of this score should be encouraged and further validated in different settings and cohorts, as it has a direct clinical impact on decision-making regarding the re-RT indication and could result into a consensual approach.

Further efforts are made to improve the prognosis of patients with recurrent brain tumors, while improving their quality of life. Some studies have suggested that the risk of radiotoxicity associated with re-RT can be mitigated by using proton beam therapy (PBT). A study by Mizumoto et al. (2013) analyzed the efficacy and toxicity of re-RT using conventional PBT versus conventional RT and stereotactic radiotherapy, in a cohort of 26 pediatric and adult patients with recurrent malignant brain tumors, including 15 (57.7%) glioblastomas multiform and 6 (23.1%) grade 3 gliomas. Toxicity outcomes showed 2 (7.7%) cases of radio-necrosis, which were well controlled in the second year following re-RT; beside minor acute toxicity events. Efficacy outcomes showed one and 2-year overall survival rates (55.4% and 45.1%) and one and 2-year local control rates (43.0% and 18.4%) respectively in the total population; and the one-year overall survival rate was higher in patients treated with PBT (75.0%) [32]. More recently, Scartoni et al. assessed the health-related quality of life among 33 patients with recurrent glioblastoma who underwent re-RT using PBT. Findings showed a clinically and statistically significant improvement in global health at the early post-re-RT phase, followed by progressive improvement in social functioning and motor dysfunction dimensions. However, a decline in the cognitive and emotional functioning was observed among these patients and was deemed as being non-significant. Further, the median PFS and overall survival were 5.9 and 8.7 months respectively [33].

Limitations

The present study is limited by the retrospective design and the small sample size which impact the external validity of the findings and conclusions. This highlights the urgent need for randomized trials and prospective cohorts to provide a more accurate evaluation of the clinical benefit of re-RT in the local population.

Conclusion

Fractioned re-RT is likely to be a safe therapeutic option for recurrent primary brain tumors, with relatively low incidence of radio-necrosis. However, its efficacy may be dependent on the pathology parameters and treatment regimen, and could be confounded with factors impacting radiotoxicity notably the maximal and cumulative radiation doses on the brain parenchyma and organs at risk. Such observations highlight the relevance for an anticipative approach to determine candidates for re-RT based on predicted safety-efficacy profiles by weighing the benefits in overall and progression-free survival with the adverse effects and other relevant parameters of quality of life. There is unmet need for conducting further randomized trials and prospective cohorts to evaluate more accurately the clinical benefit of re-RT in the local population.

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