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Dose escalation with simultaneous integrated boost for un-methylated multiple glioblastoma

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ABSTRACT

Background: Simultaneous involvement of multiple distinct brain regions occurs in 2–5% of all high-grade gliomas (HGG) and is associated with poor prognosis. Whereas radiotherapy (RT) is an important and well-established treatment for high-grade glioma, the role of dose-escalated radiotherapy has yet to be established. In this case series, we report upon the dosimetry, adverse effects, and response in patients with multiple un-methylated high-grade gliomas receiving dose-escalated radiation.

Materials and methods: We reviewed charts of patients with multifocal high grade glioma treated at our institution since January 2022. All patients had stereotactic biopsies after an magnetic resonance imaging (MRI) contrast-enhanced with T1, T2, FLAIR sequences and were discussed in a multidisciplinary oncology team. MGMT-positive patients received either TMZ alone or RT with TMZ and were excluded from this analysis. Un-methylated patients received dose-escalated RT without temozolamide (TMZ). Following computed tomography (CT) and MR simulation, the gros tumor volume (GTV) was delineated and prescribed 52.5 Gy in 15 fractions within the standard 40.05 Gy planning treatment volume (PTV). Treatment planning was volumetric modulated arc therapy.

Results: A total of 20 patients with multiple un-methylated MGMT glioblastoma multiforme were treated with dose-escalated radiation therapy between January 2022 and June 2023. All patients completed dose escalated radiotherapy without acute adverse effects. Progression-free survival at six months was 85%, as defined by the RANO criteria.

Conclusion: In this case series, we showed that un-methylated multiple high-grade glioma could be safely treated with dose escalation. Results of progression-free survival should be validated in a larger prospective clinical trial.

Key words: high-grade glioma; dose escalation; multiple glioma; un-methylated MGMT

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Introduction

Multiple high-grade gliomas represent 2–5% of all high-grade gliomas (HGG) and are characterized by the simultaneous involvement of multiple distinct brain regions. Most patients have a low Karnofsky performance status at presentation and live for a median of 4–8 months. Despite

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their disparate prognoses, current management guidelines do not differentiate between patients with multiple versus unifocal diseases. Patients with multiple gliomas are generally excluded from prospective trials. Thus, insights regarding how best to treat these patients are limited to institutional case series and database analyses [1, 2].

Radiotherapy is an essential part of standard-of-care treatment for high-grade glioma. Current guidelines recommend a dose of 60 Gy in 30 fractions or 40.05 Gy in 15 fractions in less fit patients. For elderly or frail patients, radiotherapy can be omitted, and temozolomide (TMZ) alone is offered, especially for MGMT-methylated tumors. Dose-escalated radiotherapy for high-grade glioma is an unproven strategy. Despite some meta-analyses showing a trend for improving survival with dose escalation, a recent phase 2 randomized NRG trial did not demonstrate benefit; hence, the planned phase 3 trial was canceled [3].

It is unknown whether dose escalation may benefit patients with multiple diseases or un-methylated tumors, as these patients were either excluded completely or comprised a negligible fraction of the patients studied. A retrospective study of patients over 60 treated with moderate hypofractionation showed that dose escalation with an integrated boost to 52.5Gy in 15 fractions was associated with superior overall survival (OS) and progression free survival (PFS) compared to a standard 40.05 Gy [4]. In this case series, we report the dosimetry ramifications of dose escalation, adverse effects, and response in a unique population of patients with multiple un-methylated HGG.

Material and methods

A chart review was performed of patients with a primary diagnosis of multiple HGG. All patients underwent stereotactic biopsies after an MRI contrast-enhanced with T1, T2, and FLAIR sequences, were screened for MGMT methylation, and were discussed at a multidisciplinary tumor board. Patients with Karnofsky Performance Status (KPS) scores of 90–100 were treated with both TMZ and RT, regardless of MGMT status. Treatment of patients with a KPS of 80–50 depended upon methylation status: un-methylated patients received dose-escalated RT without TMZ, whereas MGMT-positive patients received either TMZ alone or radiotherapy with TMZ. Following the completion of radiotherapy, patients were offered treatment with tumor treating fields (TTF).

The radiation protocol

The gross tumor volume (GTV) included all contrast-enhancing lesions detected on T1-weighted MRI. Clinical target volume (CTV) 1 was defined by adding a uniform 1.5 cm margin to the GTV. "Planning treatment volume (PTV) 1" was defined by adding a 3 mm margin to the GTV. PTV2 was obtained by adding a uniform 3mm margin to CTV1, in accordance with recent guidelines [5]. PTV2 was prescribed a dose of 40.05 Gy, and PTV1 was prescribed a dose of 52.5 Gy (a simultaneous integrated dose, SIB).

Patients underwent both MRI simulation and CT simulation with a thermoplastic mask. All treatments were planned using the volumetric modulated arc therapy (VMAT) technique (Eclipse version 15.6, Varian, Palo Alto, CA, USA), and image-guided radiotherapy (IGRT) was delivered using the ExacTract system (Brainlab, Munich, Germany).

Statistical analysis

Statistical analysis was conducted using IBM© SPSS© Statistics (version 26, IBM©, Armonk, NY, USA). Descriptive statistical analysis was performed for patient characteristics, radiotherapy, and dosimetry parameters. Multivariable analysis was carried out using logistic regression. Progression-free survival was assessed as the interval between initiating RT and the first imaging detection of progressive disease according to the RANO criteria in accordance with the Kaplan-Meyer method.

Adverse events

Adverse events that occurred during or after radiation treatment and were possibly attributed to treatment were evaluated and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) grading version 6.0.

Results

Population

Thirty-two patients with multiple glioblastoma multiforme were treated at our institution between January 2022 and January 2023. Four patients deteriorated rapidly and did not receive

Table 1. Patient's and characteristics and outcomes

	Multifocal un-methylated high-grade glioma (n = 20)	Multifocal high-grade glioma methylated (n = 6)
Age (median, range)	67 years (59–77)	64 (58–79)
Gender male (%)	70%	50%
KPS (median, range)	70 (60–90)	70 (60–90)
Number of lesions (median, range)	3 (2–5)	3 (1–4)
Surgery procedure Stereotactic biopsy Debulking surgery	 16 (75%) 4 (25%)	 4 (66.6%) 2 (33.3%)
PTV1 (mean, range)	68 cc (32.8–94.2)	
PTV2 (mean, range)	312 cc (114.4–478.9)	
PTV2/Brain ratio (median, range)	36.7% (21.8–46.9%)	
PFS 6 month	 85%	 66.6%

KPS — Karnovsky Performance Status; PTV — planning target volume; PFS — progression-free survival

further treatment. A total of 20 patients with un-methylated MGMT received dose-escalated hypofractionation radiation therapy. Eight patients had methylated MGMT: among them, four received TMZ alone, and four received RT + TMZ with hypofractionation.

Here, we report upon the 20 patients who were MGMT un-methylated and received dose escalation radiation alone. Patient characteristics are presented in Table 1. The median age was 67 years (range 59–77), and 70% were male. All lesions were supratentorial, and in ten patients, the lesions were confined to one hemisphere. All patients presented with a KPS between 90–60, median 70. All patients were IDH wild type. For comparison of clinical outcomes, we present the characteristics and outcomes of methylated GBM patients in the same recruitment period.

Dosimetry

The median PTV1 was 61 cc (range 32.8–94.2), and PTV2 was 301 cc (range 114.4–478.9). The median ratio between PTV2 and normal brain was 34.6% (21.8–46.9%). Dose constraints, as defined by Timmerman for 15 fractions, were met for all organs at risk [6]. Dose to the contralateral hippocampus was successfully limited to a Dmax < 14 Gy and D9 < 100% in all but one treatment plan.

Clinical course

All patients completed the radiation course. Fourteen patients (70%) had a response on subsequent MRI according to RANO criteria. Amongst the patients who had a response on imaging, ten were neurologically stable, and four demonstrated improved neurological function. Three patients were considered to have had pseudo-progression after consideration of Treatment Response Assessment Maps (TRAM) MRI and MRI perfusion sequences [7]. One patient underwent a follow-up MRI without further treatment and showed subsequent improvement. Two patients had neurological sequela as a result of increased edema, with only mild improvement observed with dexamethasone treatment. They received bevacizumab at a dosage of 5 mg/kg, resulting in improvement after three cycles and stabilization of seizure episodes.

Six months after completion of radiation, 17 of the 20 patients in our cohort had at least stable disease (85%). Among them, 11 received TTF only, two received TMZ adjuvant treatment, and four received both TTF and TMZ.

Two of the three patients with actual Progression received bevacizumab as second-line treatment. One experienced significant neurological Progression and did not advance to further treatment.

Discussion

In this case series of patients with 'multiple high-grade gliomas' treated with hypo-fractionated radiotherapy with a SIB; treatment was well tolerated and led to an 85% relapse-free survival at six months. These encouraging results surpass any previous reports of multiple high-grade gliomas.

Preclinical studies have demonstrated a dose-response relationship for radiation therapy in glioma cells. While several trials have not shown a benefit for dose-escalated radiotherapy in high-grade glioma, these trials did not include multiple un-methylated tumors [4]. In a recent publication by Perlow et al., an almost doubling of overall survival was noticed among patients who received a total dose of 52.5 Gy using a simultaneous boost. In their cohort, they did not specify data among those with multiple gliomas [4].

Hypo-fractionation has the dual advantage of achieving increased cell kill from a higher dose per fraction and reducing the effect of accelerated tumor cell repopulation by shortening the overall treatment time. These advantages may be significant in patients with 'multiple gliomas' whose aggressive tumors may have a more pronounced accelerated tumor cell repopulation.

Increased toxicity in the late-responding neural tissues is a concern that may offset the potential advantages of hypofractionation [8]. Nonetheless, our data showed that the treatment is tolerable, with only two patients requiring treatment for radiation necrosis (10%). We note a 15% pseudo-progression rate, lower than a recently published meta-analysis [9].

Our aggressive approach resulted in 85% of patients having at least stable disease after six months of follow-up, which is noticeably better than the previous series. One explanation could be that amongst patients who were still stable or had a response, none had a CDKN2A homozygote deletion or a mutation in histone K27M or H3 G34, which carry a worse prognosis [10]. Another explanation is the widespread use of TTF amongst our population (~90%).

Our study has some weaknesses, especially the limited size of the series, short follow-up and single intuition management. Further, we are unable to distinguish between the effect of dose-escalation and other factors, e.g. the use of TTF. Nonetheless, the strength of our study is that we used a prospective approach with a homogenous cohort.

Conclusions

In this case series, we demonstrate that patients with moderate-low performance status bearing un-methylated multiple high-grade gliomas can be safely treated with a hypofractionated SIB using VMAT and IGRT without TMZ. Our encouraging progression-free survival results should be validated in a larger prospective clinical trial.

Conflict of interest

Authors declare no conflict of interest.

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