



# Effects of temozolomide dosing on outcome in glioblastoma

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Received: 23 August 2025 / Accepted: 29 October 2025  
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## Abstract

**Purpose** Temozolomide (TMZ) with concomitant radiation is the standard therapy for treating glioblastomas (GBM) and is dosed based on body surface area (BSA) using a goal dose of 75 mg/m<sup>2</sup>. Neurooncologists have different methods of dosing patients, with some dosing within 5 mg of the calculated dose and others rounding to reduce patient burden. We aimed to determine the effect of rounded doses of TMZ on survival.

**Methods** We conducted a single-center retrospective review of 380 patients with GBM from 2013 to 2024. Relevant data was extracted from electronic medical records. Kaplan-Meier curves and Cox regression models were used to determine survival outcomes.

**Results** No significant impact on survival outcomes was observed when distance from the calculated temozolomide dose was analyzed as a continuous variable ( $p=0.156$ ), adjusting for MGMT, the extent of resection, radiation fractions, and Karnofsky performance scores (KPS). Even limited to just MGMT-methylated tumors, TMZ dose did not affect survival. BMI had no impact on survival outcomes. Our subgroup analysis revealed that patients with MGMT-methylated tumors, total resection, higher KPS, and  $\geq 30$  radiation fractions had improved survival ( $p<0.01$ ). Dose interruptions were not more likely with doses above 75 mg/m<sup>2</sup> (14%) than with doses at or below 75 mg/m<sup>2</sup> (9%) ( $p=0.22$ ).

**Conclusion** Rounding temozolomide doses does not significantly impact survival outcomes or risk of treatment interruptions for patients with GBM. These findings may allow neuro-oncologists to prioritize reducing pill burden and treatment costs without compromising patient outcomes.

**Keywords** Glioblastoma · Temozolomide · Dose-response relationship, drug · Antineoplastic protocols

## Introduction

Glioblastoma, a form of high-grade glioma, is the most aggressive primary brain cancer in adults [1]. Although glioblastomas are the most common primary brain cancer, they are rare in the population, with an age-adjusted incidence rate of 3.2 per 100,000 people in the United States [1]. The standard treatment includes surgical resection or biopsy and adjuvant chemoradiation [2]. There are known

prognostic factors associated with glioblastoma, such as age, performance status, extent of resection, neurological function, and MGMT promoter methylation status [3, 4]. Additionally, interruptions during chemotherapy, often due to toxicities, have been shown to negatively impact survival in patients with glioblastoma [5].

Temozolomide is an oral chemotherapy approved for use in treating glioblastomas. Dosing for temozolomide is based on body surface area (BSA), and the standard dose is calculated using the formula 75 mg/m<sup>2</sup> [2]. These chemotherapy pills come in fixed capsule sizes of 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Typically, clinical trials require the dose to be within 5 mg of the calculated dose based on the patient's BSA, however, this is not always followed in clinical practice. Due to the fixed capsule sizes, neuro-oncologists have adopted different methods of dosing patients, with some dosing within 5 mg of the calculated dose and others rounding to decrease the confusion that comes with multiple pill sizes and to reduce financial

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burden. For example, current wholesale prices for temozolomide are between \$12.52 and \$14.83 for 5 mg capsules, \$50.46 and \$57.56 for 20 mg capsules, and \$252.29 and \$287.76 for 100 mg capsules [6]. Additionally, physicians often round chemotherapy doses differently for patients based on a patient's size as measured by body mass index (BMI). Studies have found, however, that BMI has no significant impact on survival for patients with glioblastoma [7]. Additionally, two studies examined the impacts of different temozolomide doses on survival, but these studies were severely underpowered [8, 9]. However, they both found that the different doses had similar survival outcomes [8, 9]. Another study found that reducing the dosage by omitting temozolomide on the weekends negatively impacts survival for patients with glioblastoma [5]. Furthermore, MGMT-methylated tumors are expected to be more sensitive to temozolomide and thus may impact survival outcomes [4]. No study has looked at whether these subgroups of patients have impacted survival outcomes based on temozolomide dosing.

This retrospective chart review examined whether the actual temozolomide dose received, as compared to the calculated dose of 75 mg/m<sup>2</sup>, impacts survival outcomes of patients with high-grade gliomas, as no study has directly addressed this question. The secondary objectives were to determine if the actual dose received compared to the calculated dose impacts survival based on BMI and to determine if there are subgroups, based on patient or tumor characteristics, which impact survival outcomes. We hypothesized that patients who received temozolomide dosed lower than 75 mg/m<sup>2</sup> would have worse survival outcomes, and patients who received temozolomide dosed higher than 75 mg/m<sup>2</sup> would have increased toxicities.

## Methods

### Study design

A retrospective chart review at a single center was conducted. The Slicer/Dicer tool in Epic was used to identify all high-grade glioma patients treated between June 1, 2013, and May 29, 2024, who had a prescription for temozolomide in the electronic medical record. The year 2013 was chosen as the start date because this was when the first records in the EMR were available. A manual chart review was conducted to identify only those high-grade glioma patients diagnosed with glioblastoma. Data was extracted by two extractors (AR, SK) and ambiguous data was reviewed as a group.

## Variables

Demographic data was collected on patients' race, ethnicity, legal sex at birth, and age at diagnosis. The patient's diagnosis date, height, weight, MGMT promoter methylation status, the extent of resection, temozolomide, radiation dose, breaks during treatment, and the date and patient status at the last follow-up were recorded. The BMI, non-capped BSA, number of days between diagnosis and last follow-up, actual dose received, and the difference between the patient's calculated dose and the dose they received were calculated. Before beginning data analysis, the date and status of the last follow-up were updated, and patients were excluded if exclusion criteria were met. Exclusion criteria included a diagnosis besides glioblastoma, IDH mutation, temozolomide treatment without concomitant radiation, missing data, such as a temozolomide dose during radiation, and missing a height and weight within 30 days of beginning chemoradiation.

The dosing variable was calculated by determining the mg/m<sup>2</sup> the patient received by dividing the actual dose they received by their BSA. The calculated dose a patient should have received based on 75 mg/m<sup>2</sup> was calculated by multiplying 75 mg and the patient's BSA in m<sup>2</sup>. This calculated dose was compared to the actual dose the patient received in mg by finding the distance from the calculated dose. Patients who received TMZ doses below the calculated dose (x) were further categorized into three groups: (0, x-5 mg), (x-5 mg, x-20 mg), (x-20 mg, ∞).

## Statistical analysis

Demographic data were summarized using means, medians, and percentages. Univariate and multivariate Cox regression models were used to assess variables associated with survival and Kaplan-Meier curves for survival analysis. For the survival analyses, both death and discontinuation of treatment in favor of hospice care with no further follow-up were considered events. All statistical analyses were conducted using SPSS Teaching & Research (T&R 29.0.2 for Mac). Multivariable analysis included variables that had a p-value of less than 0.05, with the actual dose received as a continuous variable included automatically. Logistical regression was used to determine the relationship between treatment interruptions and survival outcomes. For a stratified analysis focused on those where dose rounding was most likely to matter, we limited to patients whose tumors were MGMT-methylated.

## Results

### Demographics

380 patients with glioblastoma were included in this study. The study population was similar to the general glioblastoma population in the United States. The average age of the study population was 62 years (Table 1), which is slightly lower than the average age of patients with glioblastoma

in the United States between 2018 and 2020 of 65 years [10]. The study population had a slightly higher male-to-female ratio of 1.66:1 (Table 1) than the overall population, which is 1.6:1 [1]. This population was more diverse with 72.7% White, 9.4% Black, 6.6% Asian, and 3.7% Hispanic or Latino (Table 1), whereas the United States glioblastoma population is 82.4% White, 6.4% Black, and 8.7% Hispanic [10]. The ethnicity of the study population was what was expected, with 8.7% Hispanic or Latino and 87.4% not

**Table 1** Demographic variables of patients ( $n=380$ )

Variable		<i>N</i>	%	Mean	St. Dev.	Median	Maximum	Minimum
Age at Diagnosis				62	12	62	87	24
Karnofsky Performance Status (%)				79	14	80	100	40
Dose of Temozolomide (mg)				144	21	140	230	100
BMI (kg/m <sup>2</sup> )				28.01	5.84	27.1	55.3	15.5
BSA (m <sup>2</sup> )				1.99	0.26	1.99	3.07	1.39
Diagnosis	Glioblastoma	380	100					
BMI Categories (kg/m <sup>2</sup> )	<18.5	5	1.3					
	18.5–25	109	28.7					
	25–30	150	39.5					
	≥30	116	30.5					
BSA Categories (m <sup>2</sup> )	<2.2	308	81.1					
	≥2.2	72	18.9					
Race	White	274	72.1					
	Black	36	9.5					
	Asian	25	6.6					
	American Indian or Alaskan Native	1	0.3					
	Hispanic or Latino	14	3.7					
	Middle Eastern	1	0.3					
	Other	22	5.8					
	No Data	7	1.8					
Ethnicity	Hispanic or Latino	33	8.7					
	Not Hispanic or Latino	332	87.4					
	No Data	15	3.9					
Legal Sex	Female	143	37.6					
	Male	237	62.4					
Extent of Resection	Biopsy	72	18.9					
	Subtotal	189	49.7					
	Total	119	31.3					
MGMT Status	Methylated	147	38.7					
	Unmethylated	209	55.0					
	No Data	24	6.3					
TMZ Calculated Dose Compared to Actual Dose	<5 mg	184	48.4					
	5–20 mg	177	46.6					
	>20 mg	19	5.0					
Radiation Fractions	15	49	13.5					
	>15 - <30	9	2.5					
	30	303	83.2					
	>30	3	0.8					
TMZ/Radiation Concomitant Therapy Interruptions (Y/N)	N	327	86.1					
	Y	38	10.0					
	No Data	13	3.9					
Status at Last Follow-up	Alive	92	24.2					
	Deceased	212	55.8					
	Hospice	76	20.0					

Hispanic or Latino (Table 1). A plurality of patients in the study population received a subtotal resection, 49.7%, followed by gross total resection at 31.3% and biopsy at 18.9% (Table 1). MGMT-methylation status was about what was expected, with MGMT-methylation of 43% in the general population compared to 38.6% methylated in the study population (Table 1) [11]. The average temozolomide dose was 144 mg (Table 1). 290 patients (76.3%) received temozolomide dosed at 75 mg/m<sup>2</sup> or lower and 90 patients (23.7%) received a dose greater than 75 mg/m<sup>2</sup> (Table 1). Of patients dosed at 75 mg/m<sup>2</sup> or lower, 48.4% were within 5 mg of the calculated 75 mg/m<sup>2</sup> dose, 46.6% were 5–20 mg lower than the calculated dose, and 5.0% were more than 20 mg lower than the calculated dose (Table 1). Most patients (83.2%) received 30 fractions of radiation, and 86.1% did not have interruptions during treatment (Table 1). Most patients were deceased or in hospice at the last follow up with only 24.2% of patients alive (Table 1).

### Univariate analysis

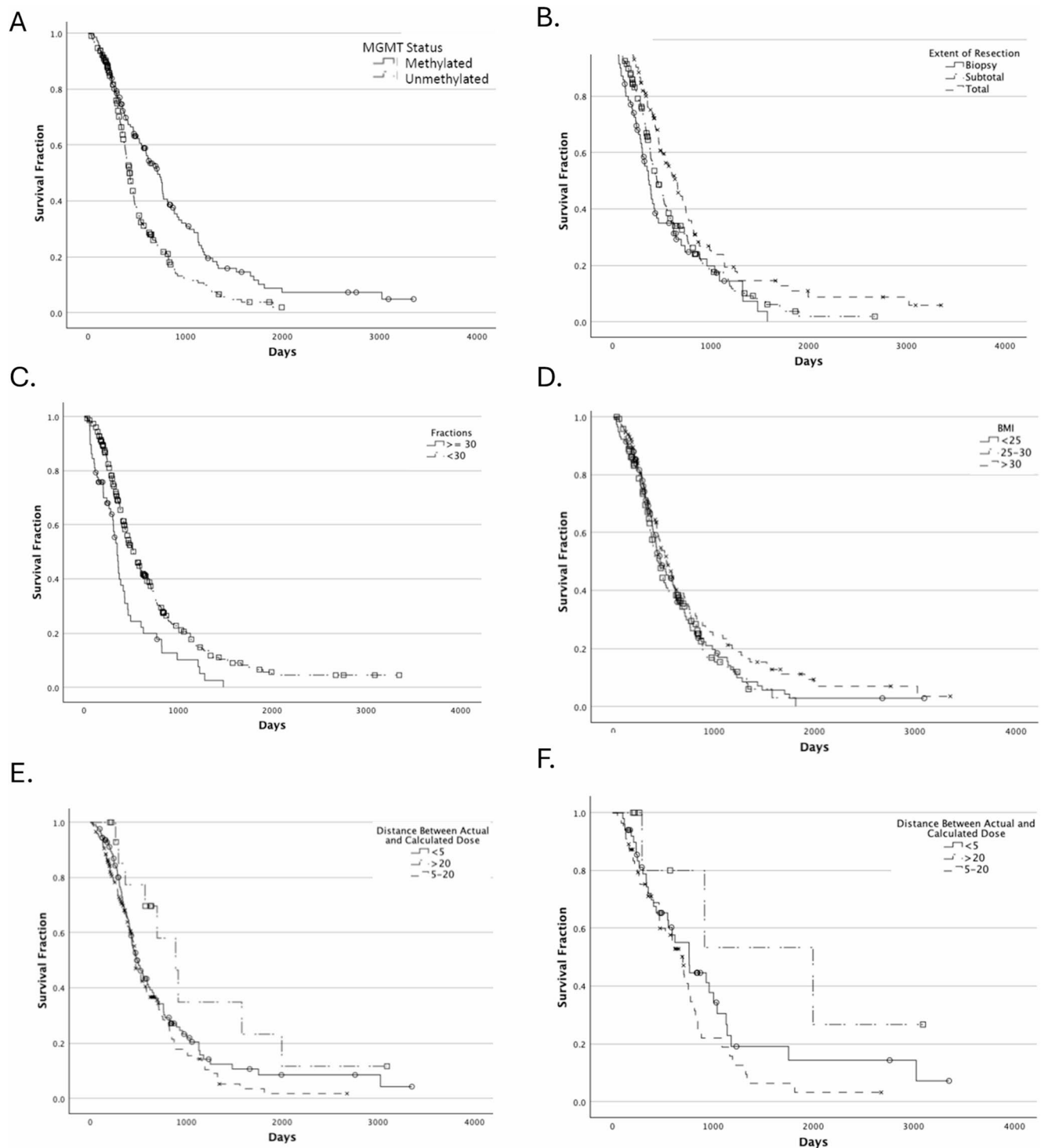
Univariate analyses are summarized in Table 2. As expected, age, MGMT promoter methylation status (Fig. 1a), Karnofsky performance status, and extent of resection (Fig. 1b) were significantly associated with survival, with p-values of

0.017, <0.001, 0.002, and <0.001, respectively (Table 2). The number of radiation fractions was also significantly associated with survival (Fig. 1c) with a p-value of 0.05 (Table 2). No significance was found regarding race, ethnicity, legal sex, or BMI (Fig. 1d).

The distance from the calculated dose of temozolomide was analyzed as a continuous variable and categorical variable. The dose of temozolomide in mg/m<sup>2</sup> as a continuous variable was not associated with survival (HR 0.99, 95% CI 0.971–1.008,  $p=0.270$ ) (Table 2). Similar results were found when looking only at patients dosed at less than or equal to 75 mg/m<sup>2</sup>. The categories of 5–20 mg *below* the calculated dose (HR 1.082, 95% CI 0.818–1.430,  $p=0.582$ ) and greater than 20 mg *below* the calculated dose (HR of 0.522, 95% CI 0.276–1.104,  $p=0.093$ ) compared to a dose less than 5 mg were not associated with survival (Fig. 1e) (Table 2). Figure 1e shows a higher than expected survival, although not statistically significant, for the group dosed at greater than 20 mg below the calculated dose. This unexpected result is likely due to a smaller sample population who were, on average, younger than the larger sample.

**Table 2** Univariate analysis using Cox regression models

Variable		Hazard Ratio	CI	Median Survival (days)	p-Value
Age	≤50	Reference		816	
	>50	1.604	1.087–2.366	556	0.017
Extent of Resection	Biopsy	Reference		391	
	Subtotal	0.619	0.438–0.876	570	0.007
	Total	0.475	0.308–0.677	775	<0.001
Distance from Calculated Dose	<5 mg	Reference		549	
	5–20 mg	1.082	0.818–1.430	659	0.582
	>20 mg	0.552	0.276–1.104	1435	0.093
MGMT Status	Methylated	Reference		775	
	Unmethylated	1.751	1.302–2.356	468	<0.001
Legal Sex	Female	Reference		623	
	Male	0.987	0.737–1.298	591	0.877
Race	White	Reference		570	
	Hispanic or Latino	1.268	0.667–2.411	519	0.469
	Black	0.751	0.441–1.278	742	0.291
	Asian	0.75	0.433–1.298	962	0.304
	Other	0.745	0.403–1.375	898	0.346
Ethnicity	Hispanic or Latino	Reference		659	
	Not Hispanic or Latino	0.951	0.585–1.547	599	0.839
Radiation Fractions	<30	Reference		366	
	≥30	0.693	0.480–1.001	605	0.05
BMI	<25	Reference		646	
	25–30	0.979	0.702–1.365	614	0.899
	>30	0.813	0.574–1.152		0.244
KPS	≤70	Reference		435	
	≥80	0.625	0.467–0.836	738	0.002



**Fig. 1** Kaplan-Meier curves of patients with glioblastoma. **(a)** Survival outcomes based on patients' tumor methylation status. **(b)** Survival outcomes based on the extent of resection of glioblastoma. **(c)** Survival outcomes based on the number of radiation fractions received as adjuvant therapy. **(d)** Survival outcomes based on patients' body mass index. **(e)** Survival outcomes comparing patients who received

temozolomide dosing within 5 mg, 5 to 20 mg, or more than 20 mg below the calculated  $75 \text{ mg/m}^2$  dose. **(f)** Survival outcomes comparing all patients with MGMT-methylated tumors who received temozolomide dosing within 5 mg, 5 to 20 mg, or more than 20 mg below the calculated  $75 \text{ mg/m}^2$  dose

**Table 3** Multivariate analysis using Cox regression models

Variable		Hazard Ratio	CI	p-value
Extent of Resection	Biopsy	Reference		
	Subtotal	0.612	0.418–0.895	0.011
	Total	0.412	0.268–0.633	<0.001
KPS	≤70	Reference		
	≥80	0.701	0.505–0.973	0.034
Radiation Fractions	≥30	Reference		
	<30	0.663	0.433–1.016	0.059
MGMT Status	Methylated	Reference		
	Unmethylated	1.732	1.274–2.356	<0.001
Distance from Calculated Dose		0.984	0.962–1.006	0.156

### Stratified and multivariate analysis

The stratified analysis looked at the distance from the calculated dose on survival outcome restricted to MGMT-methylated tumors (Fig. 1f). The stratified analysis shows no statistically significant difference between the dosing categories, with a p-value of 0.117 for those who received a dose 5–20 mg *below* their calculated dose and 0.612 for those with a dose more than 20 mg *below* their calculated dose. When restricted to MGMT-methylated tumors, dose as a continuous variable had an HR of 0.518 and a 95% CI of 0.990–0.959. The multivariate analysis included MGMT promoter methylation, the extent of resection, KPS, and radiation fractions (Table 3). MGMT promoter methylation, the extent of resection, and KPS remained significant, with p-values of <0.001, <0.001, and <0.034 (Table 3). The number of radiation fractions was not significant with a p-value of 0.059 (Table 3). The distance from the calculated dose was not statistically significant in multivariate analysis with a p-value of 0.159 (Table 3).

### Toxicities

In this study, the dose of temozolomide was examined as a continuous variable to determine if there was a correlation to an increased risk of therapy interruptions. To note, there were no dose reductions during concomitant treatment in response to toxicities. Increased temozolomide dose was not significant in increasing the risk for interruptions with a p-value of 0.810, HR of 1.005, and CI of 0.962–1.051. This study also examined the rate of toxicity within patients who received a greater than 75 mg/m<sup>2</sup> temozolomide dose and less than 75 mg/m<sup>2</sup>. Of the patients who were dosed greater than 75 mg/m<sup>2</sup>, 14% had treatment interruptions. Comparatively, of the patients who were dosed at less than 75 mg/m<sup>2</sup>, 9% had treatment interruptions. The difference

in interruptions between the two groups was not statistically significant ( $p=0.219$ ).

### Discussion

Neuro-oncologists have different methods of determining the temozolomide dose for patients with glioblastoma during radiation, the effect of which had not previously been investigated. Clinical trials typically require dosing within 5 mg of the calculated 75 mg/m<sup>2</sup> dose during radiation. However, in practice, neuro-oncologists may round to minimize pill burden or to reduce copays and some neuro-oncologists avoid rounding up out of fear of complications. The results of our retrospective analysis demonstrate no significant difference in survival outcomes in patients who received a chemotherapy dose closer to their calculated dose compared to patients who received a rounded dose. Additionally, our study shows no benefit to having a dose close to the calculated 75 mg/m<sup>2</sup> dose in subgroups defined by MGMT promoter methylation status or BMI.

Our findings are consistent with previous studies that examined the effects of different temozolomide dosing regimens on survival outcomes. While these studies were limited by small sample sizes of 160 and 86 patients, leading to underpowered results, they similarly found that patients treated with varying regimens of temozolomide had comparable survival rates [12, 13]. Additionally, our results align with a previous study that found no significant difference between BSA, BMI, and gender groups when comparing temozolomide-induced myelotoxicities [14]. The consistency in results adds credibility to the notion that individual patient characteristics may not significantly influence temozolomide toxicity profiles. However, another larger study that analyzed myelotoxicities in temozolomide treatment found that women experienced higher rates of treatment-induced toxicities [15]. This variation in results may be due to differences in the studies, where in the study mentioned above, patients were not treated with concomitant radiation and were dosed at higher rates (150–200 mg/m<sup>2</sup>). A study of 432 patients, however, found that patients on temozolomide 75 mg/m<sup>2</sup> 7 days per week during radiation had longer median survival than patients on temozolomide dosing 75 mg/m<sup>2</sup> for 5 days a week [5]. The difference in results can be explained by the large dose reduction in the previously mentioned study compared to other studies, with a 29% reduction in dose intensity between the two dosing arms. Our study had a much smaller difference in dose, with most patients receiving a dose within 20 mg of their calculated dose.

Several factors contribute to the strength of our study. Firstly, our patient population is reflective of the sample



population in previous research on temozolomide dosing as well as the population of patients with glioblastoma in the United States [1, 10, 11]. Additionally, our study showed a significant survival benefit for patients with an MGMT-methylated tumor, total tumor resection, and a higher Karnofsky performance score, reproducing commonly accepted prognostic factors. The large sample size is a critical strength of our study, increasing the statistical power of our analysis by allowing us to detect clinically meaningful differences with greater confidence. These strengths not only enhance the reliability of our results but also contribute to the generalizability and reproducibility of our findings.

Despite these strengths of our study, several limitations must be acknowledged. Our research was limited in the ability to assess temozolomide dosing during the adjuvant phase of therapy because dosing often varied by month. Furthermore, the retrospective design of our study relies heavily on the quality and completeness of medical records for accurate results. Our analysis encompassed data from various neuro-oncologists over an extended period, which may have contained inconsistencies or had unknown confounding factors. For example, there were patients in earlier years in our data set that did not have a reported IDH mutation status, although physician notes documented a glioblastoma diagnosis. These patients were included in our study with the assumption that they did not have an IDH-mutated tumor; however, this inconsistency may add variability to our results. Additionally, we noticed an unexpected result when using Kaplan-Meier survival curves to analyze the survival outcomes of patients who received a temozolomide dose more than 20 mg below their calculated dose. Although not statistically significant, this group had an inflated survival outcome compared to the other groups. This unusual finding can be attributed to the small population of patients within this category, many of whom were younger than average. Another limitation pertains to discrepancies in how weight and height were recorded for temozolomide dosing calculations. Although some neuro-oncologists recorded the exact measurements used to calculate the dose, many did not. To address this, we used weight measurements within thirty days before the first temozolomide dose, assuming that patients' weight remained stable during this period. However, for 17 patients in our sample, we did not have any weight readings within our allotted window, necessitating the use of earlier weight measurements. These inconsistencies in weight recording introduce additional variability in our analysis and may affect the accuracy of our results. Lastly, the analysis of toxicities was underpowered to detect differences of less than a doubling or more of the treatment interruption rate, which may miss small but clinically important differences.

Our findings have notable implications in treating patients with glioblastoma. Our findings indicate no significant difference in survival and toxicity profiles for rounded doses either below or above 75 mg/m<sup>2</sup>, allowing neuro-oncologists to consider reducing patients' pill burden and associated costs. Clinical trials should also consider relaxing requirements for temozolomide dosing. This has the potential to improve the quality of life for individuals diagnosed with one of the most aggressive brain cancers while contributing to the standardization of treatment. Future prospective, multi-center studies are needed to corroborate our results and establish causative relationships that will be essential in improving glioblastoma treatment practices.

**Author contributions** The conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AR, SK, ALC Drafting the work or reviewing it critically for important intellectual content; AR, SK, ALC Final approval of the version to be published; AR, SK, ALC.

**Funding** Neurosurgical Society of Virginias Medical Students Summer Research Scholarship Award (To AR).

**Data availability** Deidentified data will be made available by email to the corresponding author.

## Declarations

**Ethical approval** The study was approved by INOVA IRB with a waiver of consent and conducted in accordance with the Declaration of Helsinki.

**Competing interests** The authors declare no competing interests.

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