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Rethinking treatment de-escalation in elderly glioblastoma: Lessons from a multicenter real-world cohort

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Abstract

Background. Glioblastoma (GBM) in elderly patients (≥65 years) carries a poor prognosis and higher treatment toxicity. Consequently, many receive de-escalated regimens, often guided by MGMT promoter methylation. However, real-world outcomes across treatment strategies remain underreported and often lack molecular and functional detail.

Methods. We retrospectively analyzed 573 elderly GBM patients treated between 2009 and 2023 at 2 Israeli tertiary centers. Post-operative treatments included (1) chemoradiotherapy (CRT; 60Gy in 30 fractions or 40Gy in a15 fractions), (2) temozolomide (TMZ) monotherapy, (3) radiotherapy alone (RT), or (4) best supportive care. MGMT status and Karnofsky Performance Status (KPS) were analyzed where available. Survival was assessed using Kaplan–Meier and log-rank tests.

Results. Median overall survival (mOS) was longest with CRT (14 months), compared to 8 months for TMZ and RT monotherapies and 2 months for best supportive care. Among MGMT-methylated patients, CRT yielded mOS of 23 months versus 8 months for TMZ alone. Younger age, surgical resection, and higher KPS predicted longer survival. In the TMZ subgroup, toxicity was low (6% hematologic, 12% non-hematologic grade 3-4 events) and survival improved with increasing TMZ cycles. Salvage therapy after progression was also associated with longer survival. Limitations include retrospective design, incomplete molecular data, frailty and QOL data not collected routinely, potential selection bias, and evolving treatment practices.

Conclusion. Fit elderly patients with GBM may achieve benefit from full standard-of-care therapy. Treatment decisions should be guided by functional and clinical fitness rather than chronological age. These real-world data highlight the importance of integrating clinical and functional factors into management of elderly GBM.

Key Points

- Age alone should not guide treatment de-escalation or clinical trial exclusion.
- Fit elderly GBM patients benefit from standard chemoradiotherapy protocols.
- Extended TMZ monotherapy is associated with improved survival in selected patients.

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults, with a particularly high incidence in the elderly population (≥65 years).[1] Managing this group is uniquely challenging due to worse prognosis, increased comorbidities and increased toxicity risks.[2] As a result, elderly GBM patients are frequently undertreated, often receiving less aggressive therapy than younger patients, leading to shorter survival.[3] Given the increasing global aging population, the number of elderly GBM patients is rising, necessitating evidence-based, individualized treatment strategies.[4]

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Importance of the Study

Elderly glioblastoma (GBM) patients are often excluded from clinical trials and are frequently offered de-escalated treatment based primarily on age. However, the evidence guiding such decisions is limited. This large, real-world cohort study of 573 elderly GBM patients demonstrates that fit individuals may benefit from standard chemoradiotherapy, that extended TMZ monotherapy is associated with improved survival, and that salvage treatments can meaningfully prolong outcomes even after progression. Importantly, chemoradiotherapy was associated with survival benefit in both MGMT-methylated and unmethylated tumors. The study challenges the use of age or MGMT methylation status as sole criteria for treatment selection and emphasizes the need for individualized, performance-based decisions. These findings underscore the importance of including elderly patients in clinical trials and inform more nuanced treatment planning in this growing patient population.

The standard-of-care treatment for GBM including maximal safe resection followed by 6 weeks of radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ) (Stupp protocol)—is well established.[5] However, in elderly patients, several treatment de-escalation strategies have been explored to balance efficacy and toxicity, including hypo-fractionated RT regimens (with or without chemotherapy, for example, 40 Gy in 15 fractions or 25 Gy in 5 fractions),[6,7] TMZ monotherapy in MGMT-methylated tumors[8,9] or avoiding RT in frail patients to minimize treatment burden.[10,11] Recent advances have introduced tumor-treating fields (TTFields) as a promising non-invasive therapy for glioblastoma,[12] including in elderly patients.[13] Adding TTFields to maintenance TMZ significantly improved survival with an acceptable safety profile in elderly patients, highlighting its potential role as an adjunct or alternative in this vulnerable population. Assessing frailty is a critical component in predicting morbidity and mortality in elderly patients.[10] While most frailty scales include chronological age as a factor, age alone does not serve as a comprehensive surrogate for frailty or functional reserve.[14]

The MGMT promoter methylation status is a key prognosticator in GBM, with methylated tumors responding better to chemotherapy.[15] However, debate persists regarding the optimal testing method, and not all MGMT-methylated tumors benefit equally. New molecular classifiers, such as RTK II methylation subgroups, may refine prediction of benefit,[3,16] while single-cell studies highlight intratumor heterogeneity of MGMT methylation, cautioning against relying on a single biomarker.[17] In the ETERNITY study of long-term IDH-wildtype GBM survivors, ~75% had MGMT-methylated tumors, yet ~50% of recurrence-free long survivors were unmethylated, underscoring additional biological drivers of outcome.[18] Age-related differences in DNA repair and immune pathways have also been described[19] but are not incorporated into current clinical decision making.

Despite multiple randomized trials and meta-analyses, real-world data on elderly GBM patients receiving full standard treatment versus de-escalated regimens remain scarce.[19–23] This study is unique in comparing multiple treatment strategies across a large real-world dataset of elderly GBM patients as a function of MGMT status and Karnofsky Performance Status (KPS), often lacking in previous cohorts. We present a large TMZ monotherapy cohort and analyze the impact of salvage therapies on survival in elderly GBM patients. By integrating real-world clinical outcomes with insights from prior trials, this study aims to clarify the optimal treatment strategies for elderly GBM patients and challenge the widespread underutilization of aggressive therapy in fit elderly individuals.

Methods

Patients

We conducted a retrospective cohort study in 2 tertiary medical centers in Israel, Tel Aviv Sourasky Medical Center (TLVMC) and Sheba Medical Center (SMC). Data collection was approved by institutional review boards in both facilities (IRB 3998-17-SMC and IRB 0220-22-TLV). We searched computerized databases for patients diagnosed with histologically verified glioblastoma (glioma WHO grade IV) at age 65 or older, between 2009 and 2023. Five patients were diagnosed radiologically without histological confirmation due to contraindications for surgery. A sensitivity analysis excluding these cases showed no significant effect on OS or PFS. This limitation is acknowledged to maintain transparency regarding diagnostic certainty. Histological diagnosis was confirmed by board-certified neuropathologists following standard immunohistochemical (IHC) staining, according to the respectively updated WHO classification.[24,25] IDH1/IDH2 mutations were determined by either DNA sequencing or IHC. MGMT promoter methylation analysis was performed using a Methylation Specific Multiplex Ligation-dependent Probe Amplification based assay (MS-MLPA), by the SALSA MS-MLPA Kit ME011-rB1 mismatch repair genes (MMR) (MRC-Holland). Methylation status was calculated using the GeneMapper analysis software (Applied Biosystems) and the Coffalyser MLPA data analysis software (MRC-Holland). Five MLPA probes specific for MGMT were used to calculate the methylation status. Tumor samples in which the methylation ratio (methylated vs non-methylated DNA) was more than or equal to 0.25 were considered as methylated MGMT. Fit patients were deemed those who had the physical and mental capability to give their consent and to undergo surgery, radiation or chemotherapy treatments, had good performance status (KPS > 70%), and were free of major uncontrolled comorbidities.

Variables

For each patient, we collected the following categories of data: *baseline variables* included demographic information and performance status at time of diagnosis; *treatment-related variables* included number and extent of surgical procedures (biopsy or resection; cases where biopsy was followed by resection were classified[26] as resection). While detailed data on extent of resection (gross total vs subtotal) were available for some patients, documentation was incomplete or inconsistent for most. Therefore, for consistency, surgical procedures were analyzed using the broader categories of biopsy versus resection. Post-op treatment schedules included temozolomide (TMZ) treatment start date and number of cycles, radiotherapy treatment (RT) schedules, treatment toxicity, time of disease progression, ensuing treatment lines; and *tumor-specific variables* included histologically verified presence of IDH 1/2 mutations and MGMT promoter methylation status. Baseline KPS was routinely recorded during initial neuro-oncology and neuro-radiotherapy consultations as part of standard documentation at both participating centers, independent of trial enrollment. Disease progression was determined by treating physicians and defined as either clinical deterioration or radiological progression on contrast-enhanced MRI or CT. We defined progression-free survival (PFS) as the time from diagnosis, taken as the date of histological confirmation of GBM following biopsy or surgical resection, to disease progression or death from any cause. We defined overall survival (OS) as the time from diagnosis until death or last follow-up.

Statistical Analysis

Data were analyzed using SPSS version 29.0.2. Survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test. Categorical variables were compared between subgroups using the chi-square or Fisher's exact test, as appropriate. Continuous and ordinal variables were compared using the Mann–Whitney test or Kruskal–Wallis test. To identify independent predictors of 12-month survival, we pre-planned 2 separate Cox proportional hazards regression models. The first model was applied to the entire cohort and included key baseline variables: post-operative treatment (yes/no), age, sex, and type of surgical intervention (resection vs biopsy). The second model focused on the subgroup of patients who received post-operative treatment and additionally included baseline functional status (KPS >50%) to assess its influence on survival outcomes within treated patients. This 2-step approach allowed us to evaluate predictors both in the overall population and specifically among treated patients, reflecting differing clinical contexts. The association is reported as hazard ratios (HR) with 95% confidence intervals (CI). All statistical tests were 2-sided, and a P-value < .05 was considered statistically significant.

The chi-squared automatic interaction detector (CHAID) algorithm was applied to explore the interaction effects of clinical and demographic variables on OS. CHAID performs multi-way splits based on chi-square statistics, merging similar categories ($P < .05$), and iteratively growing the decision tree until no further significant splits are found. Variables were entered as categorical or binned continuous values.[27]

Results

Treatment Efficacy in the Entire Cohort

We analyzed EMR data from 590 elderly patients (age >=65) treated at 2 Israeli centers (2009-2023). Seventeen patients were treated at both centers, and their full treatment courses were reconstructed. The derivation of the study cohort is shown in Figure 1. The final cohort included 573 GBM patients (median age 73, interquartile range 69–76). Patients at TLVMC were younger and had better baseline status than those at SMC, resulting in higher resection rates and nearly twice the proportion receiving Chemoradiotherapy (CRT; 74.7% vs 38.5%, *Supplementary Table 1*).

Of the cohort, 105 patients (18.3%; 50 males, 55 females; median age 76) received best supportive care only (mOS 2 months). The treated 468 patients (279 males, 202 females; median age 72) had mOS of 12 months (Figure 2C), with survival rates of 29.3% at 18 months, 19.7% at 24 months, and 3% at 48 months.

Across the cohort, 157 patients (27.3%) underwent biopsy, 387 (67.5%) underwent surgical resection, 5 were treated based on imaging only, and 24 had missing data. Among those receiving oncological treatment, 121 (25.8%) were biopsied and 346 (73.9%) underwent resection: 39 patients had gross total resection, 7 underwent subtotal resection, and in 300 cases extent was unconfirmed. One patient with brainstem tumor was treated without surgery.

Median OS was significantly longer after resection versus biopsy (full cohort 13 vs 7 months; treated subgroup 15 vs 9 months; both $P < .0001$, Figure 2D). No sex-based survival differences were observed (full cohort mOS 10 months for both sexes, $P = .92$; treated patients mOS 12 vs 13 months, $P = .09$). Twelve patients were alive at last follow-up; 9 were lost to follow-up.

Post-operative treatment regimens included chemoradiotherapy (CRT): either 60 Gy in 30 fractions or 40 Gy in 15 fractions, with concurrent temozolomide (TMZ) 75mg/m^2 QD 42d/21d, respectively followed by adjuvant TMZ 150-200 mg/m^2, days 1-5, q28d. Chemotherapy alone (Upfront TMZ): same dosing as adjuvant TMZ, without radiation. Radiotherapy alone (RT only): same fractionation as in CRT, without chemotherapy.

CRT was the most common regimen (349 patients, 60.9% of the entire cohort; 205 males, 143 females; median age 70), associated with mOS of 14 months and mPFS of 6 months (Figure 2A and B). Upfront TMZ was given to 74 patients (12.9%; 40 males, 34 females; median age 77), with mOS of 8 months and mPFS of 4 months. RT only was given to 38 patients (6.6%; 30 males, 8 females; median age 76), with mOS of 8 months and mPFS of 3 months. An additional 7 patients (1.2%) received other post-operative treatments (eg, bevacizumab or RT combined with nivolumab, Supplementary Table 2).

Patients receiving CRT had significantly longer mOS and mPFS compared to RT only or upfront TMZ (mOS 14 months vs 8 months; mPFS CRT 7 months, vs 3 and 4 months; all $P < .0001$, Figure 2A and B). Notably, the upfront TMZ group consisted mainly of patients with MGMT-methylated tumors, unlike the CRT group.

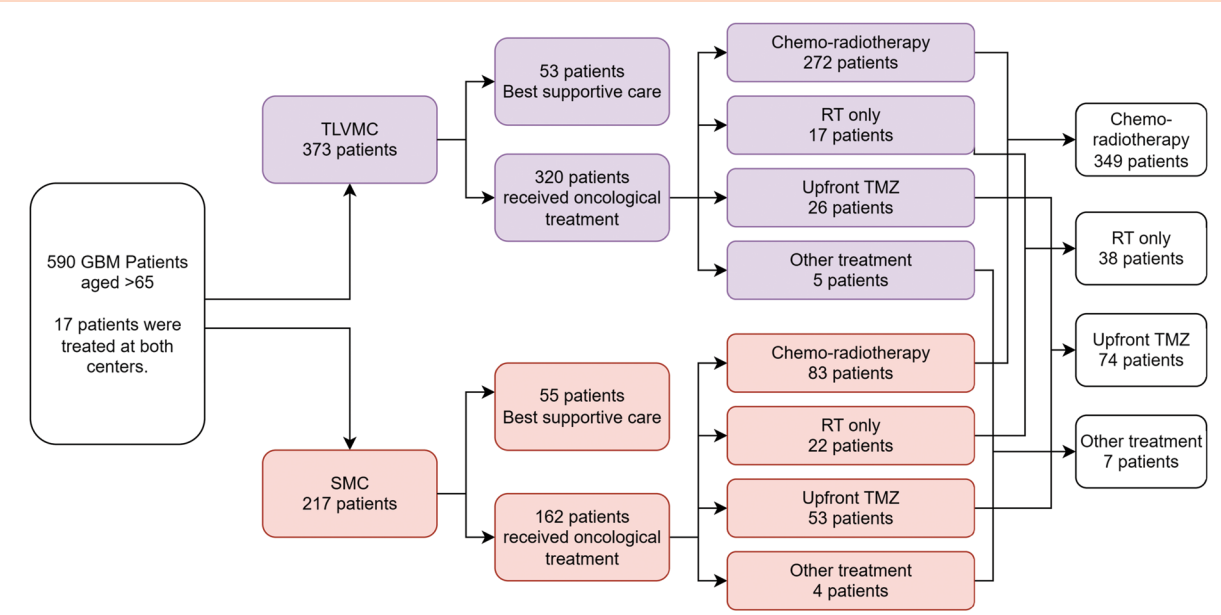

Figure 1. Cohort derivation flowchart for elderly GBM patients. The figure shows the inclusion and treatment classification of 590 patients aged ≥65 diagnosed with glioblastoma at 2 Israeli medical centers (TLVMC and SMC) between 2009 and 2023. Seventeen patients were treated at both centers and their records were reconciled to avoid duplication. Patients were categorized by post-operative treatment received: best supportive care (no post-operative treatment), chemoradiotherapy (CRT), radiotherapy (RT) alone, upfront temozolomide (TMZ), or other therapies. *Other therapies* include treatments such as bevacizumab, radiotherapy combined with nivolumab, or other non-standard regimens. Final treatment group totals after merging data from both centers are shown on the right.

Age and Functional Status Subgroup Analysis

To empirically determine an optimal age cutoff associated with OS, we performed CHAID analysis on treated patients, which identified 72 years as the optimal age cutoff: OS was 13 months for ≤72 versus 11 months for ≥73 (log-rank $P<.005$, Figure 2E). PFS was also longer in younger patients (6 vs 5 months, $P<.05$).

CRT patients were significantly younger (Kruskal–Wallis $H=102.72$, $P<.0001$), more likely to undergo resection (Fisher's exact test, $P<.0001$), and had higher KPS at diagnosis (Kruskal–Wallis $H=35.6$, $P<.0001$) than either upfront TMZ or RT only patients. Within CRT, CHAID analysis identified KPS ≥70% as prognostic: OS 16 months versus 11 months ($P<.005$), though PFS was similar (6 months).

IDH Status

IDH status was validated for 305 patients (52.3% of the entire cohort), including 61.8% (216/349) of CRT patients, 74.3% (55/74) of upfront TMZ group and 78% of RT only group (30/38). IDH mutations were rare (9 patients, 1.5%), 7 in the CRT group and one in each of the other groups. Among CRT patients, IDH mutation had mOS of 25 versus 14 and mPFS of 7 versus 6 months for IDH-WT.

Upfront TMZ Cohort Characteristics

Patient characteristics are summarized in Table 1, and treatment details in Table 2. Of 74 patients, 47% underwent biopsy and 37% had gross total resection. At diagnosis, 30 patients (40%) had KPS < 50% (Table 1). Two patients lacked definitive GBM histology: one diagnosed with "high-grade glioma" and another with "anaplastic gemistocytic glioma." IDH1/2 WT was confirmed in 74.3% (mostly via immunohistochemistry for IDH1), and MGMT promoter methylation was confirmed in 93% (69/74). Five patients with unknown MGMT status received first-line TMZ due to advanced age (74-85 years), poor performance status, and high tumor burden that would have required extensive radiotherapy fields (Supplementary Table 3).

Treatment Efficacy by MGMT Status

MGMT status was available for 191 CRT patients (54.7%; 58 positive, 133 negative) and 23 RT only patients (52%; 5 positive, 18 negative); we report further analysis only from MGMT verified patients. Among CRT-treated patients, MGMT-methylated tumors had better outcomes (mOS: 23 vs 13 months, $P<.0001$; mPFS: 8 vs 6 months, $P<.005$; Figure 3A and B).

Within MGMT-methylated patients, those treated with CRT showed superior OS (23 vs 8 months, $P<.0001$) and PFS (8 vs 4 months, $P<.0001$; Figure 3A and B) to those treated with upfront TMZ. Groups significantly differed in baseline: CRT patients were younger (median age 70 vs 77 years, Mann–Whitney $U=636$, $P<.0001$), more likely to have undergone resection ($\chi^2=9.98$, $P<.005$), and had higher KPS at diagnosis (Mann–Whitney $U=1078$, $P<.0001$).

Within MGMT-unmethylated patients, those treated with CRT again showed superior OS (13 vs 8 months,

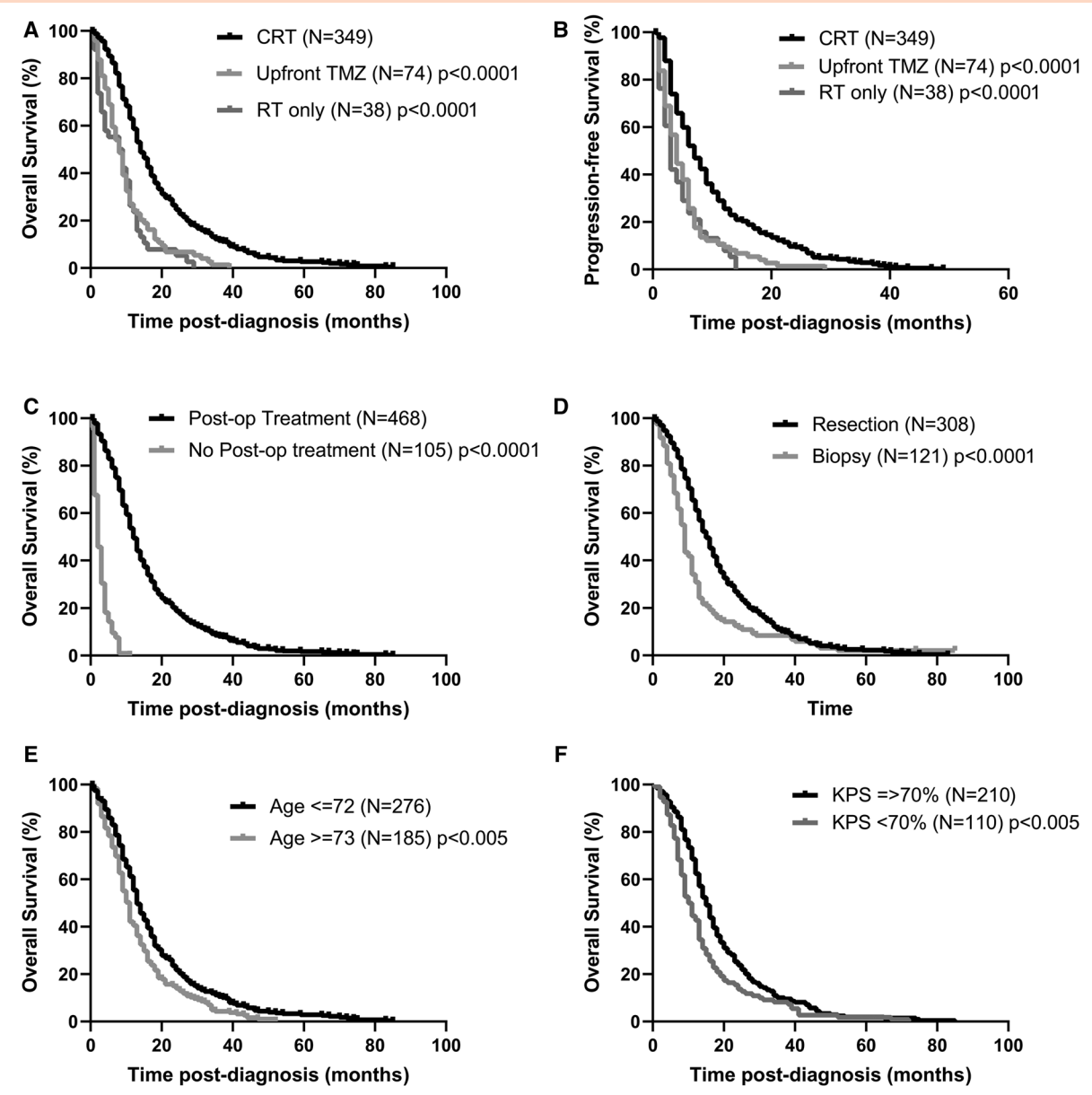

Figure 2. Survival analyses across treatment regimens and clinical subgroups. (A) Overall survival (OS) among elderly GBM patients who received chemoradiotherapy (CRT, $N = 349$), upfront temozolomide (TMZ, $N = 74$), or radiotherapy (RT) only ($N = 38$), showing significantly improved outcomes with CRT ($P < .0001$). (B) Progression-free survival (PFS) for the same groups, again favoring CRT ($P < .0001$ for both comparisons). (C) OS comparison between patients who received post-operative treatment ($N = 468$) and those who did not (N=105), showing markedly improved survival with treatment ($P < .0001$). (D) OS stratified by surgical intervention: resection ($N = 308$) versus biopsy ($N = 121$), with resection associated with significantly better survival ($P < .0001$). (E) OS comparison by age group: patients aged ≤72 ($N = 276$) versus ≥73 ($N = 185$), with younger patients showing better outcomes ($P < .005$). (F) OS comparison by performance status: KPS ≥70% ($N = 210$) versus KPS <70% ($N = 110$), demonstrating significantly improved survival with higher functional status ($P < .005$).

$P < .005$) and PFS (6 vs 3 months, $P < .05$; Figure 3C and D) to those treated with RT only. As above, groups also differed in key characteristics: RT-only patients were older (median age 77 vs 71 years, Mann–Whitney $U = 356$, $P < .0001$), all were resected (30% of CRT patients were biopsied), and had lower KPS at diagnosis (Mann–Whitney $U = 680.5$, $P < .05$).

A control analysis within the CRT group comparing MGMT-methylated and MGMT-unmethylated patients revealed no significant differences in age, extent of surgery, or KPS at diagnosis.

Treatment Efficacy and Toxicity in the Upfront TMZ Cohort

Patients received between 1-12TMZ cycles (Table 2). Among the 15 patients who received only oneTMZ cycle, treatment

Table 1. Clinical and pathological characteristics of patients treated with upfront temozolomide (*N*=74)

Total patients *N*=74	
Age	***N* (%)**
65-70	7 (9.3)
71-75	20 (27)
76-80	28 (37.3)
81-94	19 (25.3)
Sex	
Male	40 (54.1)
Female	34 (45.9)
Histology, *N* (%)	
Glioma Grade IV	72 (97.2)
Anaplastic gemistocytic astrocytoma	1 (1.3)
High-grade glioma	1 (1.3)
MGMT methylation, *N* (%)	
Yes	69 (93.2)
No	0
Unknown	5 (6.7)
IDH1/2, *N* (%)	
WT	55 (74.3)
Mutation	1 (1.3)
Unknown	18 (24.3)
Diagnosis by, *N* (%)	
GTR	28 (37.8)
STR	5 (6.7)
Resection (extent N/A)	5 (6.7)
Biopsy	35 (47.2)
Radiology	1 (1.3)
KPS at diagnosis, *N* (%)	
10%-20%	12 (16.2)
30%-40%	18 (24.3)
50%-60%	14 (18.9)
70%-80%	16 (21.6)
90%-100%	12 (16.2)
N/A	2 (2.7)

Abbreviations: GTR = Gross total resection; IDH = Isocitrate dehydrogenase; KPS = Karnofsky Performance Score; MGMT = O6-methylguanine-DNA methyltransferase; N/A = Not available; STR = Subtotal resection.

Table 2. Treatment characteristics of the upfront temozolomide (TMZ) cohort

First-line TMZ number of cycles (*N*)		
1	15	
2-5	43	
6+	16	
Second-**line treatment scheme** (*N*)		
Surgery	3	
Surgery + CRT	3	
	RT scheme (total radiation/fractions)	***N***
	60/30	2
	40/15	1
Bevacizumab	18	
	Number of cycles	***N***
	1-2 cycles	5
	3-4 cycles	3
	5-6 cycles	6
	7-8 cycles	3
RT plus TMZ	4	
	RT scheme (total radiation/fractions)	***N***
	60/30	1
	40/15	2
	35/5	1
Radiotherapy alone	13	
	RT scheme (total radiation/fractions)	***N***
	40/15	8
	35/5	2
	30/10	3
Treatment lines, *N* (%)		
1	33 (44.5)	
2	41 (55.5)	
3+	11 (14.8)	

Abbreviations: CRT = Chemoradiotherapy; Gy = Gray (unit of radiation dose); RT = Radiotherapy; TMZ = Temozolomide.

discontinuation was attributed to death (*n*=3), disease progression (*n*=4), or toxicity (*n*=4) (Supplementary Table 4). Patients who received 2 or more TMZ cycles survived significantly longer than patients who received a single TMZ cycle (9 vs 3 months; log-rank *P*<.0001, Figure 4A), and their performance status at diagnosis was significantly better (Mann–Whitney, *U*=280.5, *P*<.05). Survival outcomes stratified by baseline KPS within the TMZ-treated cohort are presented in Supplementary Table S8. Patients who received ≥6 TMZ cycles (*N*=16) had significantly longer survival than those who received 2-5 cycles (mOS 18 vs 8 months, *P*<.0001; Figure 4B). This association remained significant when analyses were stratified by MGMT status, including both MGMT-methylated patients and those with missing MGMT data. To address potential immortal time bias, we performed a 30-day landmark analysis including upfront TMZ patients who survived >30 days (*N*=60), which confirmed the observed dose–response relationship. TMZ treatment toxicity was 6% for grade 3-4 hematological events and 12% grade 3-4 non-hematological events (Supplementary Tables 5 and 6).

Upon disease progression, second-line therapy was administered to 41 patients (55.4%, see treatment types in Table 2 and outcomes by second-line treatment in *Supplementary Table 7*) while 33 patients received best supportive care. A subset of 11 patients received a third treatment line upon further progression, including bevacizumab (BEV, 4 patients), RT (3 patients), RT plus TMZ (1 patient), only TMZ (1 patient), surgery followed by BEV (1 patient), and PCV followed by BEV (1 patient).

Receiving salvage treatment was associated with significantly longer OS (4 vs 10 months; *P*<.0001, Figure 4C), and post-progression survival (PPS; 59 vs 131 days, *P*<.0001, Figure 4D). Baseline KPS did not differ between patients who received salvage treatment and those who did not (Mann–Whitney, *U*=573, *P*=.4), but KPS at progression (available for 63 patients) was significantly

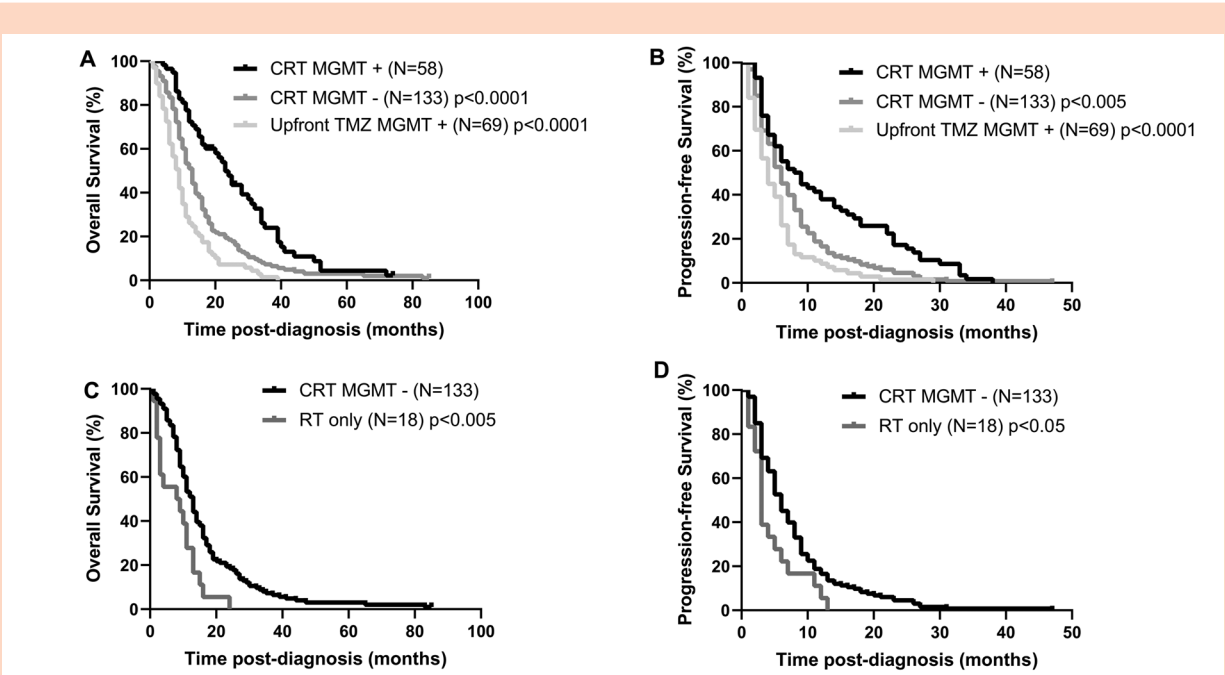

Figure 3. Overall and progression-free survival by treatment modality and MGMT promoter methylation status. (A) Overall survival (OS) among MGMT-methylated patients treated with CRT ($N = 58$), MGMT-unmethylated patients treated with CRT ($N = 133$), and MGMT-methylated patients treated with upfront TMZ ($N = 69$). CRT with MGMT methylation was associated with significantly improved OS ($P < .0001$). (B) Progression-free survival (PFS) in the same 3 groups, showing superior outcomes in the CRT MGMT-methylated group ($P < .005$ vs CRT MGMT–; $P < .0001$ vs TMZ). (C) OS comparison between MGMT-unmethylated patients treated with CRT ($N = 133$) and those treated with RT only ($N = 18$), showing significantly better survival with CRT ($P < .005$). (D) Corresponding PFS curves for the same groups as in panel C, again demonstrating improved outcomes with CRT ($P < .05$).

higher among those who received additional treatment (Mann–Whitney, $U = 252.5$, $P < .005$). OS and PPS by type of salvage treatment are detailed in Supplementary Table 7.

To explore predictors of survival within the upfront TMZ group, we conducted a CHAID analysis including age, sex, surgical intervention type, number of TMZ cycles, and KPS at diagnosis. The most significant predictor was number of TMZ cycles, with 1 cycle associated with mOS of 3 months ($N = 15$), 2-5 TMZ cycles associated with mOS of 8 months ($N = 43$), and 6 or more TMZ cycles associated with mOS of 19 months ($N = 16$). These findings were confirmed using Kaplan–Meier analysis (log-rank $P < .0001$ for all pair-wise comparisons, Figure 4B).

Multiple Regression Analysis of Predictors of 12-Month Survival

Given a median OS of 10 months in the entire cohort, we performed a Cox proportional hazards regression to identify variables independently associated with survival at 12 months. In the first multiple regression model, applied on the entire cohort, the predictors included post-operative treatment (Y/N), age, sex, and surgical intervention type (resection vs biopsy). The model was statistically significant ($\chi^2(4) = 342.5$, $P < .0001$). Post-operative treatment was strongly associated with improved survival (HR = 0.13, 95% CI [0.09–0.18], $P < .0001$), resection was associated with longer survival compared to biopsy (HR = 1.65, 95% CI [1.29–2.09], $P < .0001$), and younger age also predicted better survival (HR = 1.037, 95% CI [1.015–1.059], $P = .001$). Sex was not a significant predictor (HR = 0.84, 95% CI [0.66–1.06], $P = .14$).

In a second multiple regression model, applied to the treated subgroup, predictors included age, sex, surgical intervention, and performance status (KPS over 50% at diagnosis). This model was also significant ($\chi^2(4) = 48.15$, $P < .0001$). Resection remained a positive predictor of survival (HR = 1.66, 95% CI [1.25–2.20], $P < .0001$), KPS > 50% was associated with better outcomes (HR = 0.54, 95% CI [0.41–0.71], $P < .0001$), and again younger age predicted improved survival (HR = 1.029, 95% CI [1.002–1.057], $P < .05$). Sex was not statistically significant (HR = 0.77, 95% CI [0.58–1.02], $P = .07$).

Discussion

Elderly patients with GBM pose distinct treatment challenges, leading to studies that explore treatment de-escalation strategies. Prospective trials have tested approaches such as omitting chemotherapy, shortening radiotherapy/chemoradiotherapy courses, or offering upfront chemotherapy in patients with MGMT-methylated tumors.[7–9,28] However, many of these studies excluded full standard treatment (Stupp protocol) as a control, reinforcing a clinical paradigm where elderly patients often receive less intensive therapy than younger individuals. A notable exception is the EF-14 trial, which tested the addition of TTFields to maintenance TMZ. Although not specifically designed for

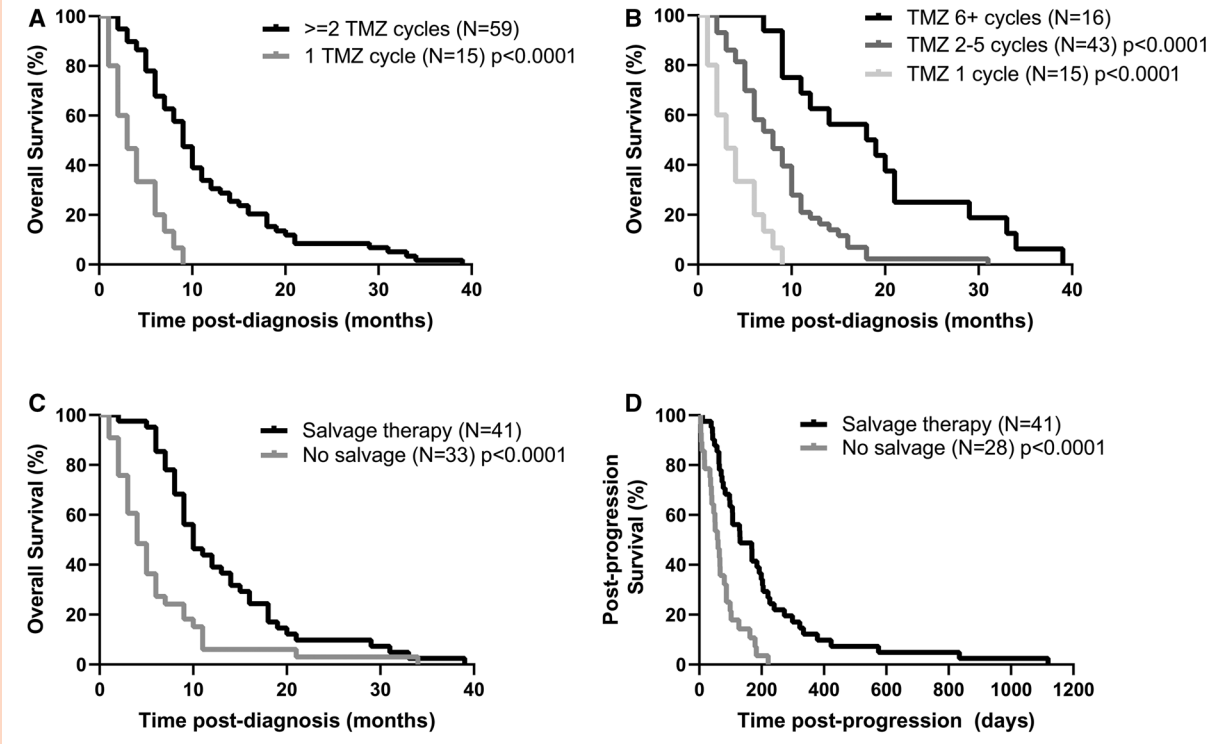

Figure 4. Survival outcomes within the upfront temozolomide (TMZ)-only cohort. (A) Overall survival (OS) by TMZ exposure: patients receiving ≥2 cycles ($N = 59$) showed significantly improved survival compared to those receiving only 1 cycle ($N = 15$; $P < .0001$). (B) OS further stratified by number of TMZ cycles: 6+ cycles ($N = 16$), 2-5 cycles ($N = 43$), and 1 cycle ($N = 15$), showing a dose-dependent survival advantage ($P < .0001$). (C) OS by salvage therapy at progression: patients receiving salvage treatment ($N = 41$) had significantly longer survival than those who did not ($N = 33$; $P < .0001$). (D) Post-progression survival (PPS, in days) in patients with known progression status, showing a significant survival advantage to those who received salvage therapy ($N = 41$) to those who did not ($N = 28$; $P < .0001$).

older adults, subgroup analyses suggested comparable efficacy in elderly patients as in younger ones.[12,13]

Retrospective real-world studies in GBM patients offer valuable insight into the comparative effectiveness of treatment strategies but are often limited by missing data on key variables like functional status (KPS), treatment toxicity or MGMT methylation status. For example, Rusthoven et al.[9] demonstrated a survival benefit of combined RT and TMZ over monotherapy in 16,717 newly diagnosed GBM patients aged >= 65, yet lacked MGMT methylation data. Similarly, Al Feghali et al.[1] analyzed 48,919 newly diagnosed GBM patients over 60 but reported KPS data for 6% of patients (3,231) and MGMT methylation data for 12% (5,884). Despite these limitations, both studies consistently showed that combined chemoradiotherapy was associated with improved OS compared to single-modality treatments.

Despite widespread clinical use, real-world data on outcomes of TMZ monotherapy in MGMT-methylated elderly GBM patients remain limited and under-reported. While randomized trials such as NOA-08[8] and the Nordic study[9] have established that TMZ alone is a reasonable option in patients with MGMT promoter methylation, these studies enrolled highly selected patients and lacked direct comparison to full standard-of-care regimens. In daily practice, Upfront-TMZ therapy is frequently chosen based on age or performance status, sometimes even without formal MGMT testing or comprehensive geriatric evaluation.[4,22]

In this real-world context, the apparent survival advantage observed among patients receiving the full protocol (CRT) likely reflects baseline differences in age, performance status, and surgical extent, rather than a causal treatment effect. CRT-treated patients in our cohort were significantly younger, fitter, and more frequently resected than those receiving monotherapy or best supportive care, emphasizing the role of selection bias in retrospective analyses.

Our analysis bridges the gap between evidence from clinical trials and real-world oncology practice, demonstrating how treatment decisions in elderly GBM are influenced by patient characteristics rather than rigid age thresholds. We analyzed a large cohort of elderly patients treated in 2 tertiary medical centers in Israel (N=573, Figure 1). Key findings include (1) any form of post-operative oncological treatment improves survival compared to best supportive care[22,23] (Figure 2C); (2) more aggressive surgical interventions significantly prolong survival compared to biopsy-only approaches (Figure 2D); (3) patients receiving the combined chemo-radiotherapy protocols achieve significantly longer OS than those receiving TMZ or RT monotherapy (Figure 2A and B); (4) MGMT-methylated tumors have better prognosis than unmethylated tumors (Figure 3A and B); (5) IDH-mutated tumors have better prognosis than IDH-WT tumors under the same treatment; and (6) salvage therapies at progression are associated with prolonged survival (Figure 4C and D). These findings align closely with previously published

studies, supporting the notion that our cohort is broadly representative of the elderly GBM population.

Chronological age is an important predictor of survival. In our cohort, patients aged 72 and older had the most pronounced reduction in overall survival (Figure 2E), even though we initially defined "elderly" as those ≥65 years. Across published studies, thresholds for defining elderly vary widely, from 60[9,21], 65[8,28], 70[7,30], 75,[31] or 80[23,32] years. These findings highlight that optimal age cutoffs may differ across populations, and suggest that age alone should neither exclude GBM patients from clinical trials nor serve as the sole basis for selecting de-escalated treatment in routine care.

As with all retrospective analyses, ours may be subject to several limitations, including selection bias, incomplete data (eg, MGMT status, IDH mutations, extent of surgery), and practice changes over time (eg, introduction of TTF, WHO grading updates). While our multivariable Cox models adjusted for key prognostic variables available, other potential confounders, including comorbidities, tumor size, and tumor location, were not consistently recorded and could not be reliably included. Consequently, residual confounding remains possible, and causal inference cannot be made from these findings. The treatment selection process (Supplementary Figure 1) reflects the interplay of clinical judgment, patient status, and in some cases, patient or family preference, which shaped treatment allocation in this real-world setting.

In Israel, all standard-of-care treatments for GBM are fully covered by the national health insurance system; therefore, treatment selection in our cohort was not influenced by patient out-of-pocket costs. TTFields use was rare in our cohort, as it only became covered by Israeli national health insurance in 2020, late in the study period (2009-2023). Another limitation is that our detailed characterization focused primarily on the TMZ monotherapy subgroup, with less comprehensive data available for other treatment groups. These limitations underscore the importance of prospective studies with standardized collection of comorbidity indices, detailed imaging data, and functional assessments.

Despite these limitations, the large sample size and the consistency of our findings with published literature support their relevance for informing the management of elderly GBM patients. Importantly, these results should be viewed as descriptive and hypothesis-generating, reflecting real-world associations shaped by treatment decisions at the time, rather than as evidence of isolated treatment effects.

MGMT Methylation

MGMT methylation is a well-established predictive biomarker for TMZ efficacy, and has often been used to justify de-escalation of therapy in frail or older individuals.[15] We compared outcomes in MGMT-methylated patients who received either CRT or upfront TMZ (Figure 3A and B), and in MGMT-unmethylated patients who received either CRT or RT only (Figure 3C and D). As expected, patients selected for CRT protocols were significantly younger, more likely to have undergone resection, and had higher KPS at diagnosis. Consequently, OS was significantly longer in patients treated with CRT in both MGMT-methylated and unmethylated groups. Notably, even MGMT-unmethylated patients receiving CRT (Figure 3C) experienced an OS benefit. Among MGMT-methylated patients, CRT was associated with substantially longer survival than TMZ monotherapy (23 vs 8 months), highlighting that MGMT methylation alone should not dictate monotherapy selection in patients who can tolerate combined treatment.

These findings underscore challenges in reliability and consistency of MGMT testing, recently discussed by Hegi et al.[16]: methodological variability (eg, methylation-specific PCR versus pyrosequencing,[33,34] or intratumor heterogeneity[17] in MGMT methylation) - can lead to discordance or inaccurate classification. Based on our findings, CRT should remain the preferred approach for fit elderly GBM patients regardless of MGMT methylation. Future studies, such as those inspired by the recent CANTON trial,[35] which demonstrated a survival benefit for adjuvant—but not concurrent—TMZ in anaplastic astrocytoma, should be prospectively investigated in GBM populations, with systematic inclusion of elderly patients.

TMZ Treatment Efficacy and Toxicity

In the subgroup of 74 patients receiving upfront TMZ, a dose–response relationship was observed: patients receiving 2-5 cycles had a median overall survival (mOS) of 8 months, compared with 19 months for those receiving ≥6 cycles (Figure 4A and B). Sixteen percent of patients had a baseline KPS of 10%-20%, indicating very poor functional status. TMZ was generally well-tolerated, with grade 3-4 hematologic toxicity in 6% and non-hematologic toxicity in 12% of patients (Supplementary Table 5), lower than rates >20% reported in prior elderly GBM studies.[8,9,36,37] Data on TMZ cycles in the CRT group were incomplete, precluding subgroup comparisons by fractionation schedule.

These findings suggest that extended TMZ may provide a survival benefit in elderly GBM patients. However, selection bias is likely, as patients who tolerate and respond to therapy are more likely to continue treatment. Prior studies in general GBM populations—including multiple meta-analyses[38–40]—have examined standard CRT (with 6 adjuvant TMZ cycles) to prolonged adjuvant TMZ. Retrospective studies have suggested a dose effect, although this has not been confirmed in randomized trials.

The inclusion of patients with very low KPS reflects real-world decision-making, where TMZ may be offered as a low-toxicity option based on patient or family preference. KPS alone may not fully capture neurological deficits, overall disease burden, or potential for treatment benefit. The observed low toxicity is unlikely to reflect selective inclusion of fitter patients and may partly result from the dosing schedule used (150-200 mg/m^2 D 1-5 q 28 D), which resembles the Stupp adjuvant protocol and may be more tolerable than metronomic regimens (eg, 100 mg/m^2 D 1-7 q 14 D). Overall, extended TMZ appears feasible in elderly patients, and concerns about toxicity should not automatically preclude its use in carefully selected individuals.

Salvage Treatments

In our cohort, among elderly GBM patients who experienced progression, those who received additional therapies

(eg, re-irradiation, TMZ rechallenge, or bevacizumab) had significantly longer overall survival and post-progression survival compared to those who did not (Figure 4C and D). Patients who were eligible for salvage treatment had significantly higher KPS at progression, whereas KPS at diagnosis was comparable between groups. Selected patients undergoing palliative re-irradiation or re-resection also benefited from improved symptom control and potentially improved quality of life.

These findings—alongside other real-world studies[23,29,41]—demonstrate a meaningful survival benefit from administering second-line or salvage treatments, even in elderly patients. Age alone should not exclude patients from additional treatment options. Instead, performance status, symptom burden, and organ reserve should guide individualized decisions. Even in the context of poor prognosis, appropriately selected patients can benefit from salvage intervention, underscoring functional status—not age—as a key determinant of eligibility for further therapy. Future research should aim to identify reliable predictors of benefit from second-line therapy and to explore integration of formal geriatric assessment tools into progression-phase treatment planning.

Prognostic and Clinical Factors Guiding Treatment Decisions

Several recent reviews have proposed conceptual frameworks to guide treatment decisions in elderly GBM patients, aiming to balance therapeutic efficacy with tolerability. Historically, treatment intensity was often dictated by age alone. In contrast, contemporary approaches emphasize multifactorial decision-making that incorporates performance status, extent of resection, MGMT methylation, and increasingly, assessments of frailty and comorbidity. The present study does not propose a new decision-making framework; rather, it places our real-world findings in the context of these previously published approaches.

Wick et al.[4] advocate for defining "elderly" not solely by chronological age, but through a combination of factors such as KPS, Charlson Comorbidity Index, and frailty assessments tools such as G8 or IDAL. Their framework suggests that fit elderly patients (KPS > 70%, MGMT-methylated) may be considered for standard chemoradiotherapy, whereas frail patients with unmethylated tumors may be better suited for hypo-fractionated radiotherapy or supportive care. Similarly, Pellerino et al.[2] propose risk-stratified approaches in which patients aged 65-69 with good KPS are candidates for the full Stupp protocol, while those ≥70 are assessed for suitability to the Perry regimen (short-course RT with TMZ). In frail patients, MGMT methylation assumes a more central role in treatment selection, supporting TMZ monotherapy if methylated, or RT alone if unmethylated.

Although KPS is widely used to measure general functional status, it may not adequately reflect how functional status is influenced by neurologic deficits common in GBM patients. In our TMZ-only subgroup, KPS at diagnosis predicted the number of TMZ cycles completed, but not the likelihood of receiving salvage treatment upon progression. This observation suggests that scales specifically designed for neurological assessment, such as NANO43 scale or MRC neurological scale[44] may offer greater sensitivity and clinical relevance in neuro-oncology settings.[45,46]

Mason et al.[7] and Mazarakis et al.[1] further emphasize that treatment decisions must remain individualized, highlighting both the limitations of current molecular markers and the importance of shared decision-making involving patients and caregivers—particularly when weighing survival gains against risks such as toxicity and cognitive decline.

Taken together, these frameworks reflect a broader shift toward personalized and stratified care in elderly GBM integrating clinical, molecular, radiological, and geriatric parameters. However, real-world implementation of such models remains limited, and prospective validation in diverse clinical settings is required. Accordingly, our findings should be viewed as illustrating how established prognostic factors interact in routine practice, rather than as supporting a specific decision algorithm.

Conclusions

Our data suggest that chronological age should not be the sole determinant of treatment decisions in elderly GBM patients. While age remains a prognostic factor, fit older adults may achieve survival outcomes comparable to younger patients when treated with standard-of-care regimens such as the Stupp protocol.

Although many trials in the elderly have supported dose-de-escalation strategies, these often lacked a full-treatment control arm. Treatment intensity should therefore be guided by individualized assessments of frailty, comorbidities, and functional status rather than by age alone. The same principle should apply to clinical trial design: elderly patients should not be excluded solely on the basis of chronological age.

Importantly, the retrospective nature of this study precludes causal inference and is subject to inherent selection bias. In addition, incomplete MGMT and IDH profiling and the absence of formal assessments of frailty, neurocognition, or quality of life limit the scope of our conclusions. These limitations highlight the need for prospective studies that systematically integrate clinical, molecular, and functional factors to refine patient selection and optimize treatment strategies.

MGMT promoter methylation remains a key predictor of benefit from chemoradiotherapy, yet our findings indicate that selected patients with unmethylated tumors may still derive meaningful survival advantages from combined treatment. Future research should incorporate emerging biomarkers—such as DNA damage response signatures and TERT promoter mutations—alongside performance and frailty indices to achieve more personalized, patient-centered care in this population.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa)

Keywords

elderly GBM | temozolomide | MGMT methylation | chemoradiotherapy | real-world data

Author Contributions

L.Z., O.F., and A.T. conceived the study and designed the analysis (Conceptualization, Methodology). L.Z., A.B., F.B., D.T.B., and A.T. contributed clinical data (Resources). O.F., E.F., I.D., and O.S.S. collected and curated the clinical dataset (Investigation, Data Curation). O.F. performed the statistical analysis, supervised the project, and wrote the first draft of the manuscript (Formal Analysis, Supervision, Writing—Original Draft). All authors reviewed and revised the manuscript (Writing—Review & Editing).

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Ethics Statement

This study was approved by the Institutional Review Boards of Tel Aviv Sourasky Medical Center and Sheba Medical Center. Informed consent was waived due to the retrospective nature of the study.

Data Availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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