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RESEARCH

Optimizing the Stupp protocol for treatment of glioblastoma: eliminating age bias, enhancing treatment timing, use of stereotactically-guided sequential boost, and dexamethasone dosing

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Abstract

Background The Stupp protocol is the standard of care for glioblastoma, yet implementation remains inconsistent, particularly regarding age selection, treatment timing, dexamethasone dosing, and usage of stereotactically-guided sequential boost (SGS-Boost). This study evaluated how treatment intervals, dexamethasone exposure, and sequential fractionated radiotherapy boost affect survival, with emphasis on eliminating age bias.

Methods We retrospectively analyzed 269 patients meeting the 2021 World Health Organization criteria for glioblastoma treated at our institution. Of these, 173 patients underwent maximal safe resection followed by chemoradiotherapy, and adjuvant temozolomide was planned. Following stratification by O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status, we examined treatment timing, SGS-Boost, dexamethasone exposure, and adjuvant temozolomide cycles. Cox multivariable analysis was performed on key parameters to elucidate relationships between these factors.

Results Stupp protocol completion significantly improved OS in both methylated and unmethylated populations ($p < 0.0001$). In methylated patients, both initiating chemoradiotherapy 32–49-days post-surgery and adding SGS-Boost independently improves outcome ($p < 0.0001$). Poor outcomes were found when dexamethasone was given at ≥ 1.2 mg/m^2 at critical treatment points. Cox multivariable analysis confirms the importance of timing of steps and dexamethasone dosages during chemoradiation, adjuvant temozolomide, and pre-palliatively. Importantly, patients ≥ 70-years-of-age who undergo maximal safe resection and chemoradiation have identical outcomes to equivalently-treated younger patients.

Conclusions Optimizing treatment intervals including timing of onset of chemoradiation, incorporating a SGS-Boost in methylated patients, minimizing dexamethasone, and eliminating age bias significantly improves survival. Refinements of the Stupp protocol maximize therapeutic benefit.

Key points

Completing the Stupp protocol improves survival in glioblastoma across all age groups.

Optimal timing enhances outcomes in all patients and stereotactically-guided sequential boost enhance outcomes in *MGMT*-methylated cases.

Dexamethasone < 1.2 mg/m^2 improves survival outcomes in both methylated and unmethylated patients, especially during the final week of chemoradiation.

Keywords Dexamethasone · Glioblastoma · Stupp protocol · Stereotactically-guided sequential boost

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Introduction

Since the publication of the Stupp protocol [1], advancements have been made regarding diagnosis and treatment of glioblastoma. However, implementation remains inconsistent, particularly regarding therapeutic timing, radiotherapy modalities, and use of adjunct medications. Additionally, the original Stupp trial included a heterogeneous patient population, some of whom would fail to meet the 2021 WHO diagnostic criteria for glioblastoma [2]. In prior reports [3], patients aged ≥ 70-years are often excluded from the Stupp protocol [4, 5].

Dexamethasone is used to manage edema, particularly at diagnosis and during the perioperative period. Dosing practices prior to chemoradiation vary, but radiation oncologists often taper to the greatest extent before chemoradiotherapy [6]. Paradoxically, managing edema with dexamethasone may worsen outcomes due to its immunosuppressive effects [7, 8].

This study is centered around five critical questions.

First, is failure to deliver the Stupp protocol associated with demographic factors, and if so, is this justified?
Second, are there optimal treatment timing intervals aid outcomes?
Third, does an SGS-Boost aid survival?
Fourth, to what extent do dexamethasone levels impact outcome?
Fifth, does extending the use of adjuvant temozolomide from 6 to 12-cycles improve survival?

Materials and methods

Study design and patient selection

After Institutional Review Board approval, our Health Data Science and Analytics Center identified 717 potential patients with glioblastoma treated at our institution (2016–2024). Patients were excluded if their medical records lacked sufficient information or if pathology reports indicated IDH-mutations, 1p/19q co-deletions or prior astrocytoma [1, 9–13]. Figure 1A shows a flow diagram for patient selection. Individual patient characteristics and treatment profiles are in supplement S1.

269 patients met the 2021 WHO criteria for glioblastoma [2] and had adequate records available.

The glioblastoma cohort

Of the 269 patients, 241 had results from *MGMT*-promoter methylation testing.

30 patients received biopsies (including 4 patients with partial resections) and 66 underwent maximal resection, but not chemoradiotherapy (60-Gy/temozolomide), with individual treatment profiles in supplement S1.

173 patients received the Stupp protocol: maximal resection, then 60-Gy of fractionated radiotherapy with concomitant temozolomide. Methylation-status identified in 169 patients.

Patient group features tabulated in supplement S2.

Chemoradiotherapy: Conventional or with SGS-Boost

All 173 Stupp protocol patients received fractionated stereotactic radiotherapy to a total dose of 60-Gy with concomitant temozolomide (75 mg/m^2). The majority received 30 fractions of 2-Gy ($n = 112$), consistent with Radiation Therapy Oncology Group guidelines [14].

61 patients underwent a two-stage regimen with SGS-Boost. Generally, in this approach 23–25 fractions of 2-Gy were administered targeting the residual enhancing tumor and the T2 Flair abnormality with a margin, followed by 5–7 fractions at 2-Gy per fraction focused on the tumor bed and residual enhancing tumor with a 1–2 cm peritumoral margin, to a total of 60-Gy.

Adjuvant temozolomide

Of the 173 patients who started the Stupp protocol, 152 started adjuvant temozolomide, at ≥ 150 mg/m^2/day, and 99 became fully compliant by completed 6-cycles.

Dexamethasone

Patient body surface area was calculated using Mosteller's method [15].

Dexamethasone dosages were identified in patient records at three key intervals:

1. The last week of chemoradiotherapy.
2. At the first dose of adjuvant temozolomide.
3. The pre-palliative phase.

The pre-palliative phase was defined as the 6-to-8-week period prior to hospice initiation or, for living patients, to 5/1/2026.

Dexamethasone dosages were recorded in the last week of chemoradiation in 164/173 Stupp patients, in 149/153 of those who started adjuvant temozolomide and in 170/173 of those in the pre-palliative phase.

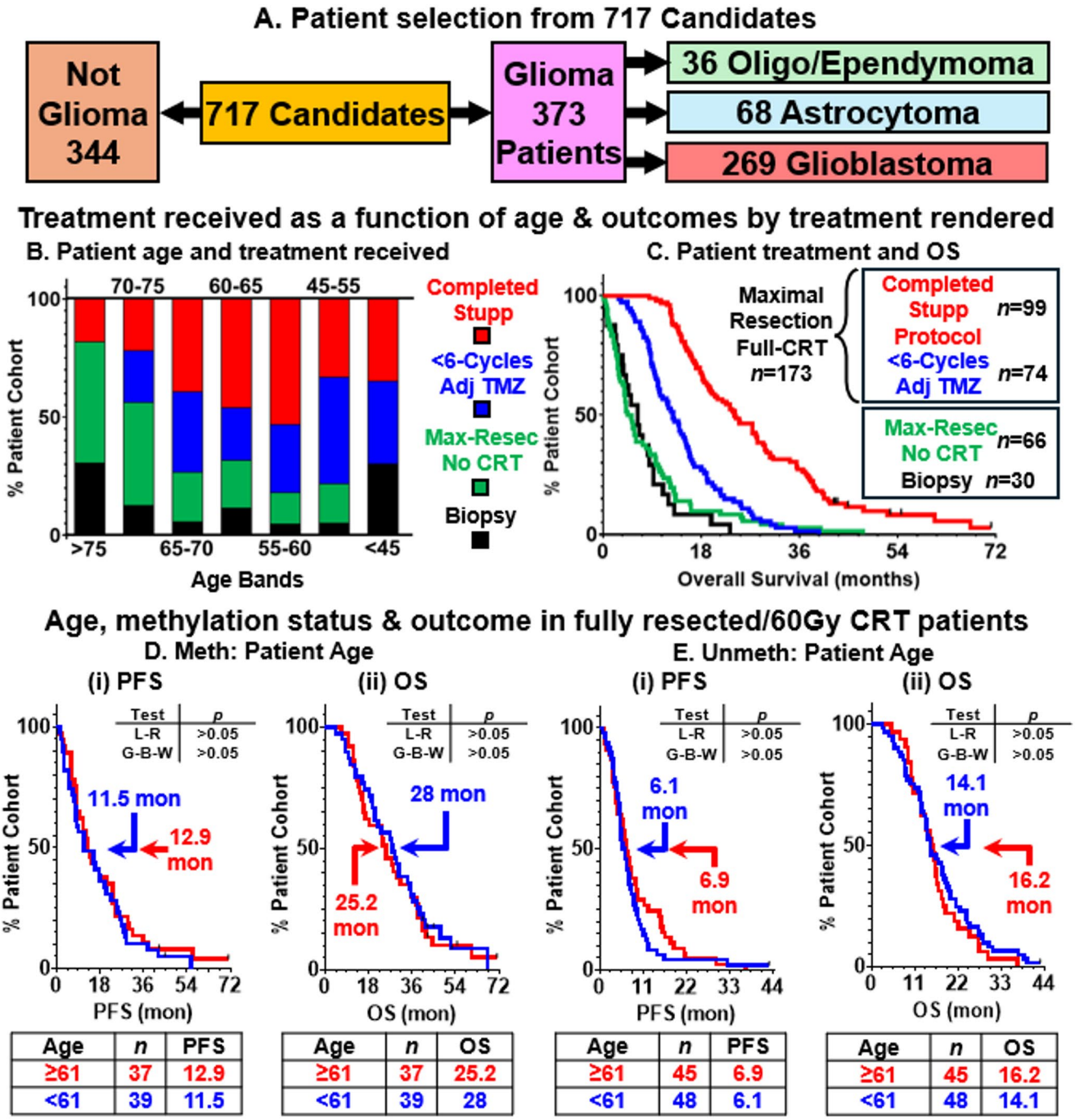

Fig. 1 Glioblastoma patient age, treatment patterns, and outcomes. **(A)** The hospital search set winnowed 717 glioblastoma patients down to 269 with pathology reports in line with the 2021 WHO inclusion criteria. **(B)** Treatment received stratified by age. Proportions of patients completing the Stupp protocol and receiving adjuvant temozolomide decline with increasing age. **(C)** Kaplan-Meier curves showing survival by treatment profile, color-coded as in panel **B**. **(D) & (E).** PFS and OS of patients with or without *MGMT* promoter methylation who underwent debulking and chemoradiotherapy, stratified at the median age of 61 years. PFS and OS outcomes were independent of age. G-B-W, Gehan-Breslow-Wilcoxon test; L-R, log-rank test; mon, months; OS, overall survival; PFS, progression-free survival

Outcomes

Overall survival (OS) was defined as the interval from initial resection until death or May 1st, 2026.

Progression-free survival (PFS) was defined as the interval between initial resection and radiologic progression.

Radiologic progression was assessed by neuroradiologists using Response Assessment in Neuro-Oncology (RANO 2.0) criteria [16, 17].

Statistical analysis

Microsoft Excel was used to perform Student's *t*-tests and Fisher's exact tests to assess continuous and categorical variables, respectively.

Kaplan-Meier survival and Cox multivariable analyses were performed using GraphPad Prism (version 9.5.1). Log-rank (L-R) and Gehan-Breslow-Wilcoxon (G-B-W) statistical tests were applied, with log-rank results reported in the text.

Cox multivariable analysis independently assessed continuous and categorical variables.

OS was used for calculating the hazard ratio.

Categorical variables examined in the 269-patient cohort were stratified at a KPS at 70 and at age ≥ 70. Tumor location in terms of bilateral, midline, or multifocal was also analyzed. Maximal resection, successful chemoradiation (60 Gy/temozolomide), ability to complete 6-cycles of adjuvant temozolomide, and MGMT promoter methylation status were also analyzed.

The categorical variables of KPS, age, and radiation dosage given during radiation/chemotherapy in these 269 patients were analyzed.

241 patients with MGMT-reportage were stratified into 105 methylated and 136 unmethylated. Cox multivariable analysis was then performed on these patients in the same manner, excluding MGMT-status.

The 77 methylated and 93 unmethylated patients who also underwent the Stupp protocol were also examined using Cox multivariable analysis. The four categorical variables examined were: surgery to chemoradiation timing (≥ 32-days), usage of < 1.2 mg/m^2 dexamethasone during the final week of chemoradiation, usage of SGS-Boost, and completion of 6-cycles of adjuvant temozolomide. Three continuous variables were examined in this MGMT-stratified pair: patient age and dexamethasone levels (as mg/m^2) at the start of adjuvant temozolomide and in the pre-palliative stage.

Results

Age, treatment provision, and outcomes

The only significant demographic factor associated with reduced receipt of the Stupp protocol was age, with less aggressive treatment in those ≥ 70 (Fig. 1B**)**.

In the cohort of 269 glioblastoma patients, 72.5% were aged < 70-years at diagnosis.

93% of those < 70-years underwent maximal resection, and the remainder who were poor surgical candidates received biopsies.

Only 78% aged ≥ 70-years received a maximal resection. Of the 22% biopsied, 70% had a KPS ≥ 70.

In these fully resected patients, the 60 Gy/temozolomide chemotherapeutic regime was initiated in 90% of patients aged < 70 years.

Only 44% of the fully resected patients ≥ 70-years received standard chemoradiotherapy, seemingly independent of tumor location or KPS.

Among the maximally resected, those ≥ 70 or < 70-years of age had similar chemoradiotherapy discontinuation rates (≈ 8%).

91% of patients < 70-years began adjuvant temozolomide after chemoradiation, compared to just 75% of patients > 70-years ($p < 0.04$).

Other than the perceived age risk, no medical contraindications were apparent in those who did not begin adjuvant temozolomide.

When adjuvant temozolomide was started, only 62% of patients < 70-years completed 6-cycles whereas 80% of patients ≥ 70-years finished ($p < 0.05$).

Treatment distribution by age of the 269-patient cohort is illustrated in Fig. 1B.

Less aggressive treatment was pursued in patients ≥ 70-years old. Overall, 42% of patients who underwent the Stupp protocol failed to complete 6-cycles. Discontinuation was due to drug toxicity (≈ 20%) or apparent radiographic progression (≈ 80%) (Fig. 1B and C).

Failure to complete the Stupp protocol results in significantly worse outcomes [4, 9, 12, 18].

The 99 Stupp-compliant patients had a median OS of 24.3-months, whereas the 74 who failed adjuvant temozolomide had an OS of 13-months ($p < 0.0001$).

Kaplan-Meier survival curves, stratified by surgical treatment, chemoradiation status and completion of 6-cycles of adjuvant temozolomide are presented (Fig. 1C).

Analysis of the Stupp protocol population

The median age of the Stupp protocol population is 60.8-years old. Following stratification first by methylation status, and then at ages < 61 and ≥ 61, delivers a pair of methylation subtypes that are age stratified into near equal *n*=numbers.

The statistical power for a Mantel-Cox/Log-rank test is described by the Schoenfeld formula [19]. A major component of the Schoenfeld formula is the term $P(1\text{-}P)$. This term is maximized, as is statistical power, when $P = 0.5$, with equal-sized groups of events [20].

When stratified by age, no differences in PFS or OS are observed between those ≥ 61-years old and those < 61, given equivalent treatment (Fig. 1D and E). We observe no statistically significant effect of patient age, at any age-stratification

point, on outcome in those treated with the Stupp protocol, in either methylation phenotype.

Timing of chemoradiotherapy

49.7% of patients began chemoradiotherapy ≤ 31-days after surgery, and the remainder began at ≥ 32-days. In patients with methylated tumors, initiation at ≥ 32-days after surgery improved OS by a year ($p < 0.05$, Fig. 2A). However, no improvement was observed in unmethylated patients.

SGS-boost

The OS of the methylated population that received SGS-Boost was nearly double that of those who received conventional chemoradiotherapy. No impact on unmethylated patients was observed with inclusion of SGS-Boost (Fig. 2B).

In the subset of methylated patients who finished 6-cycles of adjuvant ($n = 53$), those given SGS-Boost had a median OS of 40.5-months ($n = 23$). This was 17-months greater than the OS of treated with conventional chemoradiotherapy ($n = 30$, $p < 0.0001$). The characteristics of those receiving conventional and SGS-Boosted chemoradiation are shown in supplement S2.

Dexamethasone during chemoradiotherapy: BMI and BSA considerations

Only 26% of patients had a BMI within healthy ranges (18.5–25), and in the Stupp protocol cohort the median BSA was 2.0 m^2, exhibiting a range of 1.3 to 2.9 m^2.

Dexamethasone doses were given in increments of 2 mgs 79% of the time. A 2 mg pill equates to a median dosage of 0.99 mg/m^2, with a range of 0.69 to 1.42 mg/m^2. Preliminary analysis suggested a dexamethasone cut-off of > 2 mg per day. This dosage is < 1.2 mg/m^2 in ≈ 90% of patients, and the transition from 2 to 3 mgs allows a further 8% of the patients to remain below 1.2 mg/m^2. The value of < 1.2 mg m^2 was used as the cutoff in analysis, stratifying populations in ≈ 2:1, low: high, fractions.

In methylated patients, doses ≥ 1.2 mg/m^2 during the last week of chemoradiotherapy were associated with an 11-month reduction in OS ($p < 0.001$). In the unmethylated, high-dose dexamethasone reduced OS by 5-months ($p < 0.0001$, Fig. 2C).

Timing of adjuvant temozolomide

We used the first day of chemoradiation, rather than the last, as the starting point for judging the optimal timing gap before initiating adjuvant temozolomide and show *MGMT*-phenotype differences.

In methylated patients, starting adjuvant temozolomide ≥ 75-days after the start of chemoradiotherapy (> 4.6 weeks post-chemoradiation) was linked to an increase OS by > 16-months ($p < 0.01$, Fig. 2D).

Unmethylated patients followed a parabolic distribution, with optimal outcomes occurring when starting adjuvant temozolomide 65–81-days after the initiation of chemoradiotherapy (3–5 weeks post-chemoradiation). This timing improves OS by 4.5-months ($p < 0.001$), and with the chance of finishing 6-cycles rising from 50% to 75% ($p < 0.001$, Fig. 2D).

Patients with these optimal timing gaps were twice as likely to be receiving low dexamethasone (< 1.2 mg/m^2) when starting adjuvant temozolomide, ($p < 0.0001$).

Dexamethasone at adjuvant initiation

Low dexamethasone exposure, < 1.2 mg/m^2, when starting adjuvant temozolomide was strongly associated with improved survival. In methylated patients, minimal dexamethasone was associated with an improvement in PFS of 16-months and with an OS of nearly 2-years ($p < 0.0001$). In unmethylated patients, adherence to these lower dosages tracked improvement of PFS by 3-months and OS by 4.5-months ($p < 0.01$, Fig. 3A, B).

Radiological progression and continuation of temozolomide

Of the 71 methylated patients who started adjuvant temozolomide, 24/71 experienced radiographic progression before completing 6-cycles, 33.8%. Therapy was discontinued in 19 of these patients, but neurooncologists continued adjuvant therapy in 5 cases until ≥ 6-cycles were completed.

Of the 79 unmethylated who started adjuvant therapy, 45/79 experienced radiographic progression before completing 6-cycles. Pseudoprogression was suspected in 18 cases where therapy continued until ≥ 6-cycles were completed. In these unmethylated, comparing the 27 patients where adjuvant was stopped with the 18 who continued to ≥ 6-cycles, we observe no difference in PFS, but OS increased by 5-months ($p < 0.001$, Fig. 3C). The hazard of premature termination of adjuvant temozolomide due to presumed progression has previously been described [21].

Number of adjuvant cycles

No survival benefit was observed from extending adjuvant temozolomide beyond 6-cycles. The minimum time patients took to complete 12-cycles was 14-months. We selected

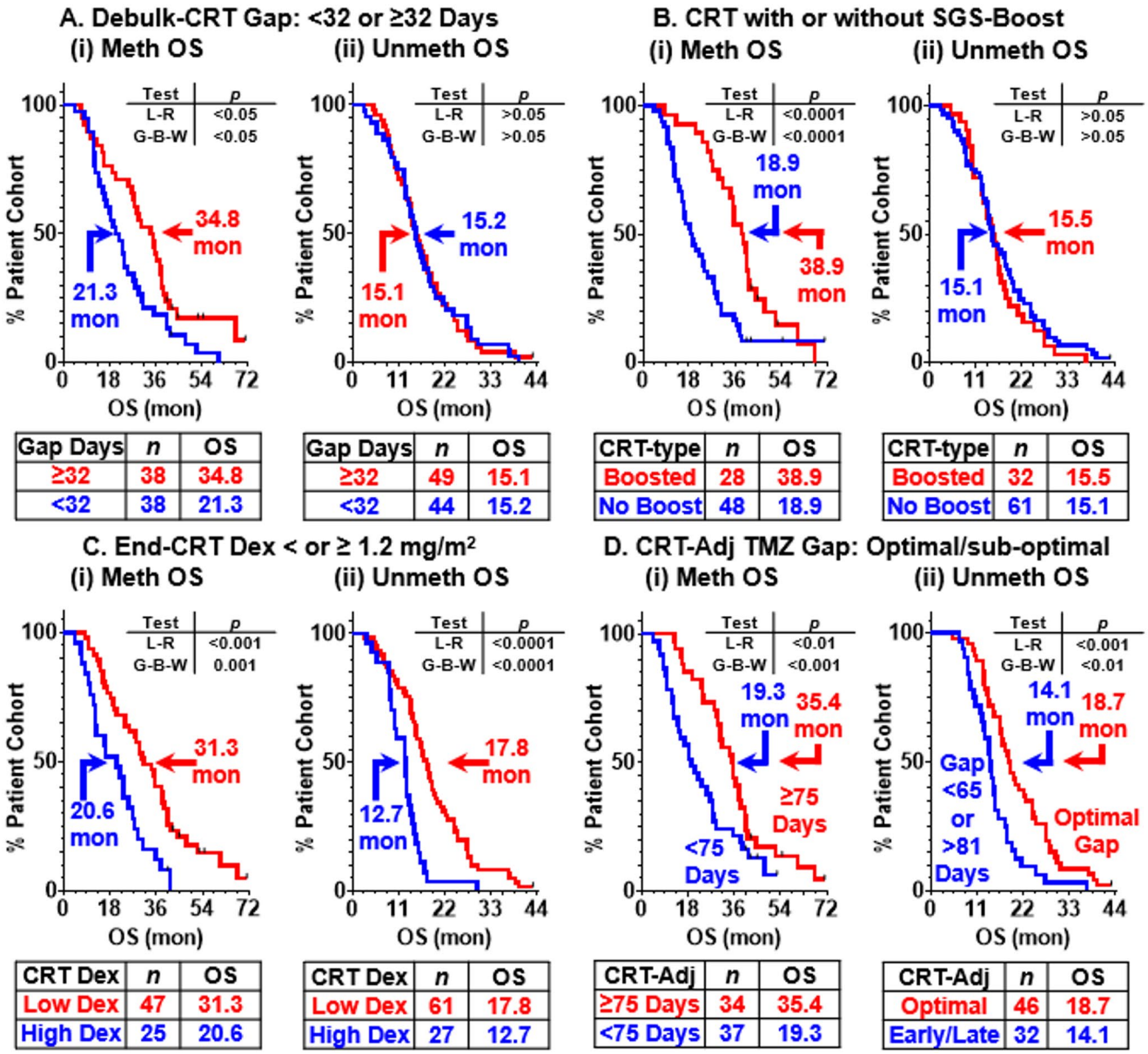

Fig. 2 Impact of treatment timing, radiosurgical boost, and dexamethasone dosage. **(A)** Kaplan-Meier curves showing survival by surgery-to-CRT timing. In *MGMT* promoter-methylated patients, initiating CRT ≥ 32 days after resection improved OS by 13.5 months. **(B)** Kaplan-Meier curves showing survival by addition of SGS-Boost during CRT. SGS-Boost increased OS by 20 months in *MGMT* promoter-methylated, but not unmethylated, patients. **(C)** Kaplan-Meier curves show survival as a function of dexamethasone use in the final week of CRT. Dexamethasone dosage at < 1.2 mg/m² in *MGMT* promoter-methylated patients provides an ≈ 11 month OS advantage. Unmethylated patients treated with low dexamethasone gain a 5-month survival advantage. **(D)** Kaplan-Meier curves showing survival by CRT-to-adjuvant temozolomide timing. A longer time window between CRT and the initiation of adjuvant temozolomide extended OS in both *MGMT* promoter-methylated (≥ 75 days) and -unmethylated (65–81 days) patients who began adjuvant temozolomide cycles. CRT, chemoradiotherapy; Dex, dexamethasone

methylated patients who had only 6-cycles but could have taken 12-cycles, with a PFS of ≥ 14-months. We compared the PFS and OS of those who completed 12 or more adjuvant temozolomide cycles with those who could have completed 12 cycles, before progression. No statistical difference is observed in either the PFS and OS curves of those taking 6-cycles and those taking ≥ 12 where PFS is matched (Fig. 3D).

Stupp protocol compliance

The Stupp protocol, when completed to 6-cycles of adjuvant, improved PFS and OS in patients (Fig. 4A, B). The median

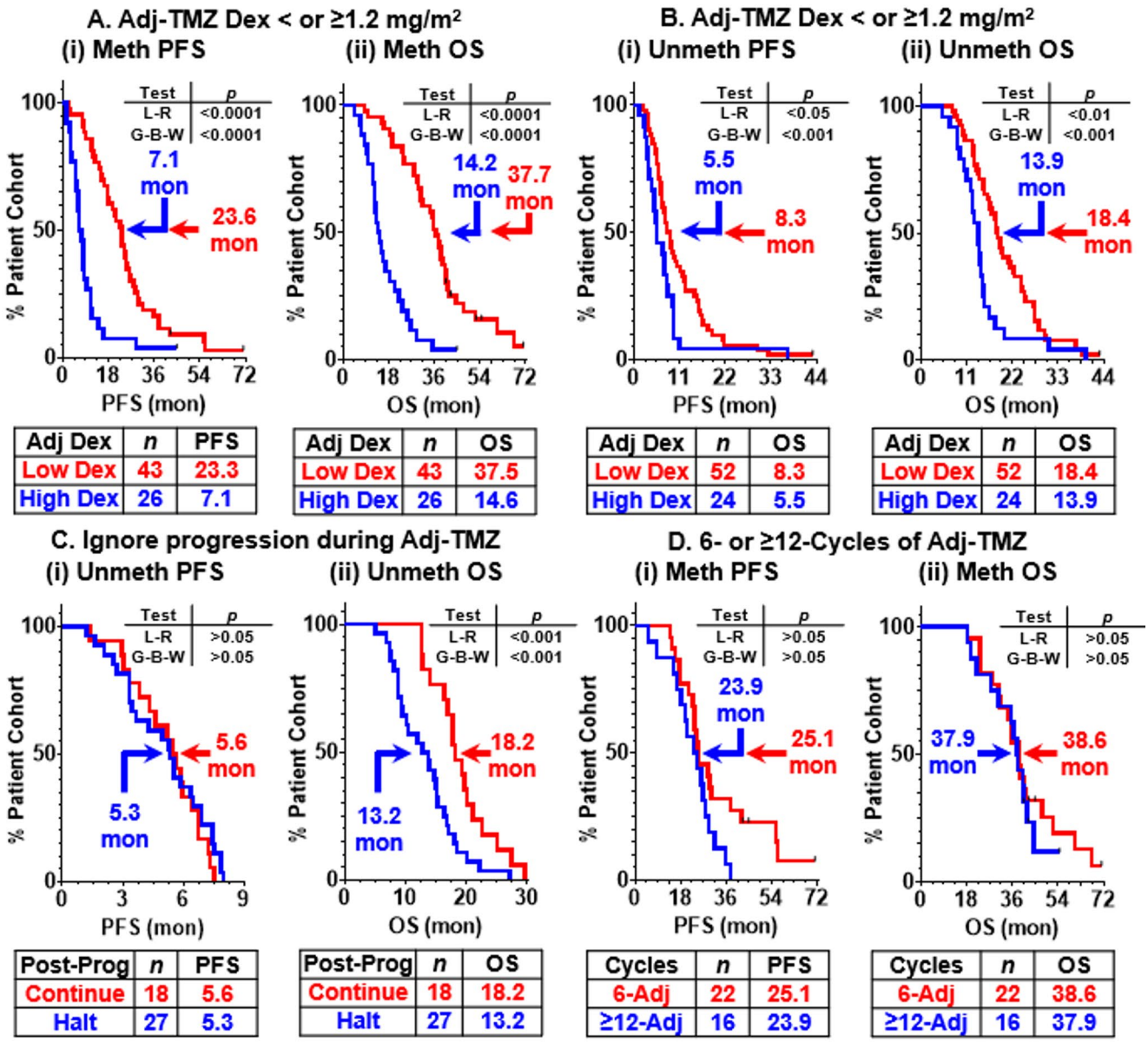

Fig. 3 Dexamethasone use with adjuvant temozolomide and impact of cycle numbers. **A. & B.** Kaplan-Meier curves show survival at low dexamethasone dosing (<1.2 mg/m^2) at the initiation of adjuvant temozolomide. Low dexamethasone starting adjuvant temozolomide is linked to an OS increase of 23.5 months in methylated and ≈4 months in unmethylated patients. **C.** Kaplan-Meier curves of unmethylated patients who underwent radiological progression before completing adjuvant temozolomide are stratified by completion of the Stupp protocol. Continuing temozolomide despite early radiographic progression extended OS by ≈5 months even though both populations have identical PFS profiles. **D.** Kaplan-Meier curves showing survival by number of adjuvant temozolomide cycles in methylated patients. Completing > 6-cycles of adjuvant temozolomide conferred no OS advantage over only 6-cycles in patient groups who would have been able to finish 12-cycles before progression. Adj, adjuvant; CRT, Dex, dexamethasone; L-R, log-rank test; Mon, months; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide

PFS was ≈23-months in compliant vs. 6-months in non-compliant methylated patients. The OS was 34.3-months in those who finished 6-cycles of adjuvant temozolomide, and only 14-months in those who did not ($p < 0.0001$).

In the unmethylated, finishing Stupp yielded a median PFS of 9.6-months and an OS of 19.5-months, compared with 6-months of PFS and 12.5-months of OS for that did not ($p < 0.0001$).

Dexamethasone in the pre-palliative stage

Methylated patients receiving dexamethasone dosages < 1.2 mg/m^2 during the pre-palliative treatment phase survived

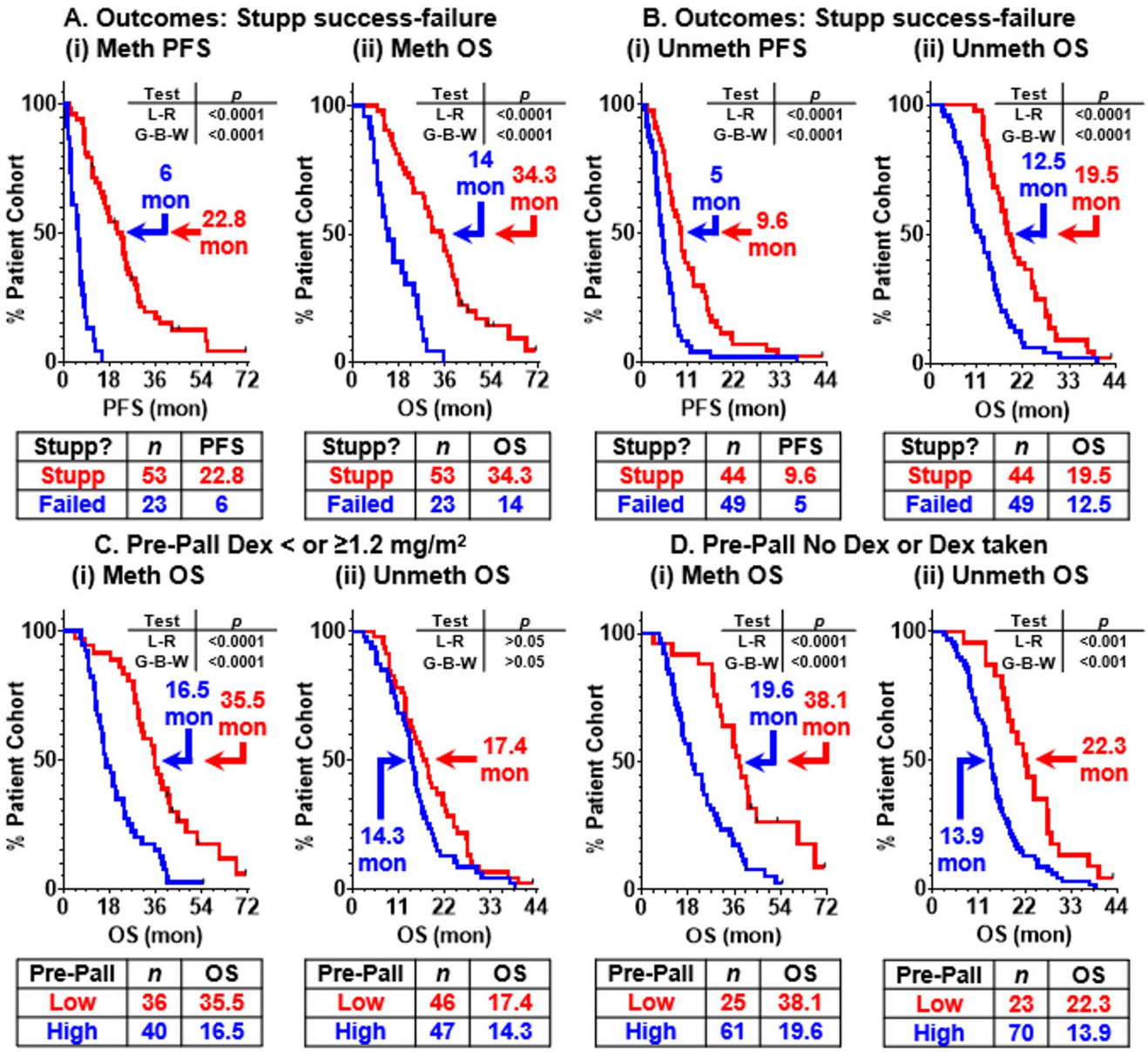

Fig. 4 Stupp compliance and during the pre-palliative treatment phase. **(A)** Kaplan-Meier curves showing outcomes based on Stupp protocol compliance in patients with *MGMT* promoter methylation. Stupp completion improved PFS by ≈17 months and OS by ≈20 months in methylated patients. **(B)** In unmethylated patients, Stupp protocol completion increases PFS by ≈5 months and OS by 7 months. **(C) & D.** Kaplan-Meier OS curves for patients stratified by pre-palliative dexamethasone. **C.** In methylated patients, levels of dexamethasone below 1.2 mg/m^2 are associated with a 19-month improvement in OS. There is a more modest increase in unmethylated patient OS which is not statistically significant. **D.** Abstaining from dexamethasone entirely increased methylated patient OS by 18.5 months and unmethylated patient OS by 8.4 months

longer, with a 19-month greater median OS ($p<0.0001$, Fig. 4C).

In unmethylated patients, there is a nonsignificant increase in median OS from 14.3 to 17.4-months.

All patients abstaining from dexamethasone completely in the pre-palliative phase do far better than those receiving dexamethasone.

In methylated patients, the dexamethasone-free OS is 38.1-months and the dexamethasone-dependent 19.6-months ($p<0.0001$). In the dexamethasone-free unmethylated patients, the median OS is 22.3-months versus 13.9-months in the dexamethasone-dependent ($p<0.001$, Fig. 4D).

Multivariable analysis

The Forest plots in Fig. 5 show OS-derived hazard ratios from Cox multivariable analysis of different patient populations, with corresponding statistical significance.

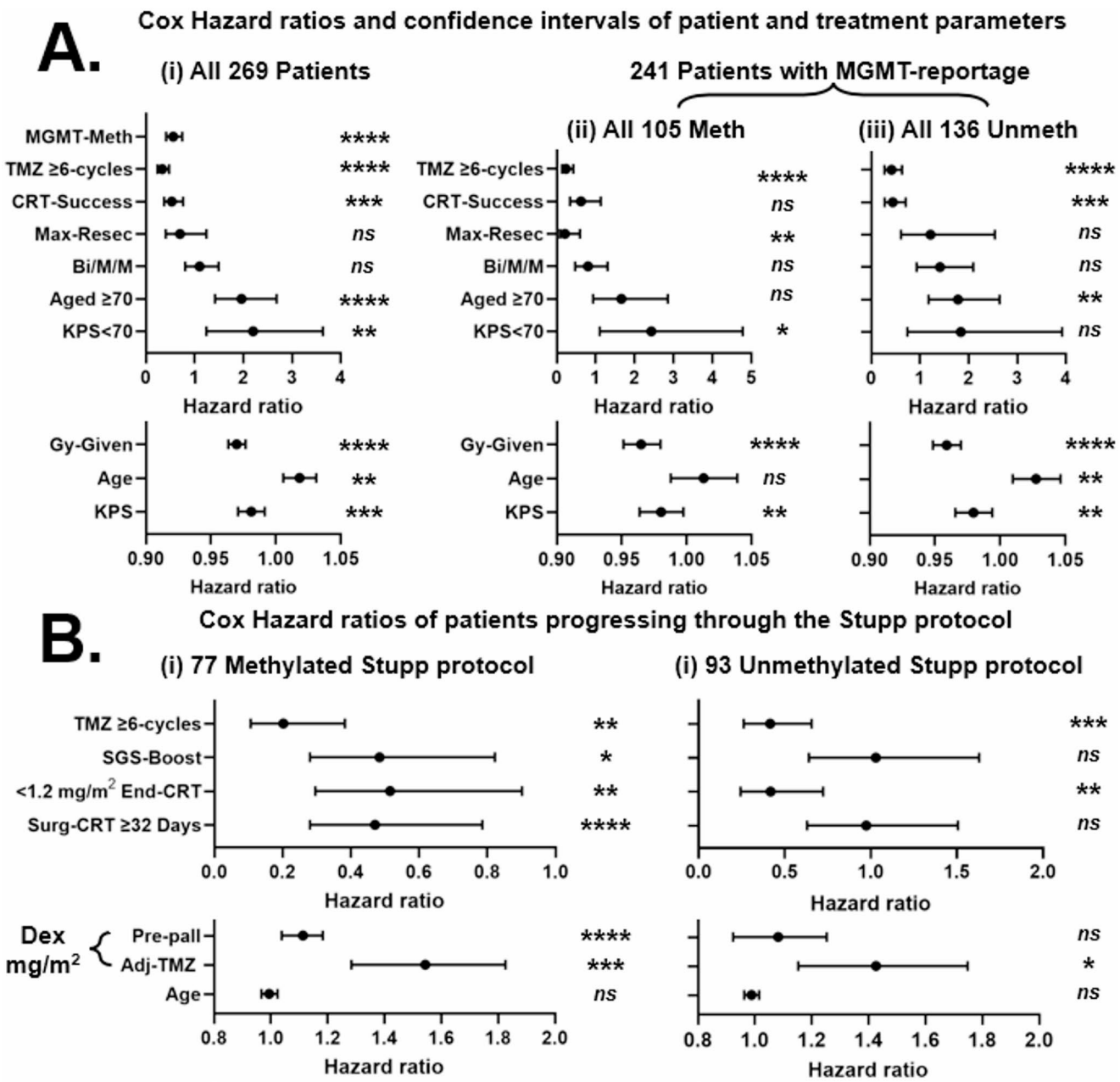

Fig. 5 Cox multivariable analysis. **A**. Multivariable analysis was used to generate hazard ratios and resultant Forest plots for patient and treatment parameters in paired sets. Analysis of categorical variables are shown in upper plots and with continuous data in the lower plots. The first pair of plots, A(i) derive from the whole 269 patient cohort that have heterogenous treatment and *MGMT*-methylation status. The paired plots, A(ii) and A(ii) analysis of populations stratified by methylation-status. **B.** Variables are presented in Stupp protocol order, with plots separated again with categorical variables at the top and continuous at the bottom. Stupp populations are stratified by methylation status, with B(i) methylated and B(ii) unmethylated. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; ****, $p<0.0001$

Plots are presented in ordered manner, from the most heterogeneous to most homogenous populations, following stratification by methylation status and treatment. Plots are also paired, with the upper plots analysis of categorical variables and lower plots of continuous variables.

Figure 5A **(i)** shows the analysis of the whole patient population ($n=269$). Categorical patient variables show that those with low KPS (<70) and those aged≥70-years do poorly, as described by others [22, 23]. In this heterogenous population, no statistically significant impact on the hazard ratio is observed with suboptimal tumor location, nor if maximal resection, rather than biopsy, was performed. Treatment with chemoradiation and with 6-cycles of adjuvant temozolomide is highly advantageous, as is tumor methylation status.

Examining three continuous variables: age, perioperative KPS, and Grays received during radiotherapy/chemoradiotherapy, we observe that patient age is associated with poor outcome, but that KPS and radiation dose given are linked with improved outcomes.

When stratified by MGMT-status, two smaller but more heterogenous populations result. Figures 5A **(ii) and (iii)** show analysis of methylated ($n=105$) and unmethylated ($n=136$) patients.

Categorical and continuous analysis of methylated patient data shows that low KPS is linked to poor outcome, but patient age is not a risk factor. Improved hazard ratios are linked to extent of resection, radiation dose, and adjuvant temozolomide completion. In these methylated patients, suboptimal tumor location does not negate therapeutic benefit.

Categorical and continuous analysis of unmethylated patients indicates increased patient age is a statistically significant hazard. Low KPS is also detrimental, but a cutoff at <70 does not capture an at-risk patient population. Neither extent of resection nor tumor location give statistically significant outputs. Aggressive treatment produces statistically significant improvements in unmethylated patient outcome, with radiotherapy dose, successful chemoradiation, and completed adjuvant temozolomide linked to improved survival.

Figure 5B is focus on Stupp protocol patients, with analysis performed on the methylated ($n=76$) and unmethylated ($n=93$). Neither population shows any effect of patient age on survival, as was the case in earlier analysis (Fig. 1D**&E**).

Methylated patients show improved outcomes with a $\geq$32 day between surgery and chemoradiation, with utilization of SGS-Boost and successfully finishing adjuvant temozolomide, Fig. 5B **(i)**. Low dose dexamethasone during key treatment steps also aids outcome.

The same analysis with unmethylated patients, Fig. 5B **(ii)**, highlights the importance of finishing 6-cycles, and maintaining low dexamethasone during chemoradiation and adjuvant temozolomide.

Discussion

Implementation of the Stupp protocol varies, with clinicians often modifying timing, radiotherapy techniques, or supportive medications. This analysis highlights several parameters that substantially influence outcomes and suggests opportunities to optimize treatment outcomes.

The median age for glioblastoma presentation in the USA is 68 years [24], in our cohort 63.3-years and the exclusion of patients $\geq$70-years may result in systemic undertreatment.

Patients older than 70 receive less aggressive treatment, a point raised a decade ago by Almenawer and co-authors in their extensive review [25]. They were more likely to undergo biopsy rather than resection, even with favorable tumor anatomy. They also were less likely to receive chemoradiation and adjuvant temozolomide.

We show in Fig. 1 and in Fig. 5 that the outcomes of the 24% of patients aged >70 who completed the Stupp protocol were directly comparable to younger patients, reflecting prior evidence of efficacy in older patients [25].

Treatment timing emerged as a critical determinant of outcome. Previous work indicated chemoradiotherapy should begin post-6 weeks of resection, but an optimal window was not defined [26]. Our data indicated that initiation $\geq$32-days after surgery maximized survival in the methylated. In Stupp compliant methylated cases, the optimum bounds were between 32 and 49-days. Methylated patients treated $\geq$32-days had low dexamethasone dependency, ($p<0.05$).

Only in methylated patients did we observe a survival advantage using SGS-Boost. The survival advantage is so large that the use of SGS-Boost in methylated patients should be the subject of a clinical trial.

The importance of adjuvant temozolomide was confirmed. In patients with methylated tumors, delaying the start of adjuvant temozolomide until $\geq$75-days after the first day of chemoradiotherapy improved both PFS and OS. 89% of those who waited for $\geq$75-days until cycle-1 were taking <1.2 mg/m^2 dexamethasone, compared with only 37% of those who started adjuvant therapy earlier ($p<0.0001$).

With unmethylated tumors the optimal window was 65–81-days ($\approx$3–5 weeks post-chemotherapy). These findings likely reflect a balance between abating post-radiotherapy inflammation and the standard treatment aggression per phenotype.

Previous reports suggest 40% of patients with unmethylated tumors have MRI scans indicating progression might instead have pseudoprogression, even if RANO 2.0 criteria suggests otherwise. In methylated patients, this may be as high as 90% [27]. Thus, Brandes and coauthors [27] suggest that adjuvant temozolomide treatment be continued, ignoring indications of progression. However, unlike the findings in Brandes, we found that extending adjuvant therapy beyond 6-cycles did not provide additional benefit, consistent with a prior meta-analysis [28].

Despite awareness of the negative impact of dexamethasone on patient outcomes, this drug remains in use because it addresses edema and neurologic deterioration [29–31]. In this study, where we normalized dosage to BSA, dexamethasone use was consistently associated with worse outcomes. Patients receiving <1.2 mg/m^2 of dexamethasone during the final week of chemoradiotherapy or when initiating adjuvant

temozolomide had better outcomes than those receiving higher doses, with total abstinence best during this and the pre-palliative stage.

These findings suggest steroid-sparing strategies, including the use of other anti-inflammatory interventions at key treatment points.

Overall, our findings support reexamining the Stupp protocol's application in contemporary practice, highlighting the importance of eliminating age bias and striving to complete the Stupp protocol in all patients, optimizing treatment intervals, incorporating a SGS-Boost during chemoradiotherapy in methylated patients, restricting adjuvant temozolomide to 6-cycles, and minimizing dexamethasone use.

Limitations

We have limited our coverage to those patients whose tumors were compliant with the 2021 WHO guidelines. We did not analyze 104 patients with glioma classifications that did not have genetic testing allowing modern categorization. This rigorous classification step may have introduced a bias in our treatment profile.

Patients treated at the Texas Medical Centre have many treatment avenues among the institutions and many undergo personalized treatment plans. This results in differences in such areas as provision of chemoradiation and adjuvant chemotherapy.

We drew data from physicians' notes. This allowed for a near-perfect reconstruction of treatment timelines but was less satisfactory for identifying confounding medications, thus lower reportage of dexamethasone dosages at key treatment points.

Our use of dexamethasone dosage, accounting for patient body surface area, is unorthodox.

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Data availability All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethical approval The examination of patient records was undertaken following institutional review board approval.

Competing interests The authors declare no competing interests.

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