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Original Article

Ultra-hypofractionated versus conventional chemoradiation for newly diagnosed glioblastoma: Survival and toxicity results of a multicenter randomized trial

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ABSTRACT

Purpose: In glioblastoma, standard first-line chemoradiation since the 2005 EORTC/NCIC trial is 30x2Gy with concurrent and adjuvant temozolomide. A phase II study suggested ultra-hypofractionation (6x6Gy) may offer comparable survival, with reduced treatment time and costs, potentially improving health-related quality of life (HRQoL). This phase III randomized trial (Netherlands Trial Registry, NL72953.041.20) evaluated non-inferiority of ultra-hypofractionated temozolomide chemoradiation in glioblastoma patients.

Patients and methods: Adults with newly diagnosed glioblastoma and a Karnofsky performance status ≥70 were randomized (1:1) to ultra-hypofractionated (6x6Gy in 2 weeks) or standard (30x2Gy in 6 weeks) radiotherapy, both with concurrent and 6 cycles of adjuvant temozolomide. The primary endpoint was 2-year overall survival (OS); the non-inferiority margin was a hazard ratio of 1.2. Secondary outcomes included progression-free survival (PFS) and toxicity.

Results: Enrollment stopped early, due to slow accrual (n=135/474 planned, 67 experimental, 68 standard). Median OS was shorter in the experimental arm: 13.0 months (95% CI 10.3-15.7) versus 21.0 months (95% CI not estimable). In a time-dependent analysis, survival was similar in the first 6 months (HR 0.99, 95% CI 0.39-2.50), but mortality was higher thereafter (HR 2.54, 95% CI 1.57-4.09, $p < 0.001$). Radiation necrosis or pseudoprogression was more frequent after ultra-hypofractionation (47.8% vs 16.2%; HR 5.20, 95% CI 2.56-10.58), with increased dexamethasone use at 6-12 months. No grade 4-5 toxicities were observed.

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Conclusion: Non-inferiority of the 6x6 Gy chemoradiation regimen could not be demonstrated. This ultra-hypofractionated regimen was associated with inferior survival and increased radiation necrosis, and therefore should not replace standard chemoradiation.

Introduction

Glioblastoma is the most common primary malignant brain tumor and has a poor prognosis, with a median overall survival (OS) of approximately 14-17 months, despite surgery and consecutive chemoradiotherapy [1,2]. Standard radiotherapy for a newly diagnosed glioblastoma has been 30 fractions of 2 Gy for over 40 years [3], with an overall treatment duration of six to seven weeks. Since the 2005 EORTC/NCIC trial this treatment has included daily concurrent, and six adjuvant cycles of temozolomide.

This prolonged treatment occupies a considerable proportion of the remaining lifespan of patients with a poor prognosis.

The burden associated with this prolonged treatment duration prompted several studies that assessed the effects of ultra-hypofractionation [4–9]: reducing the number of fractions by increasing the dose per fraction. An ultra-hypofractionated regimen, which typically includes fractions of $\geq$5 Gy, reduces hospital visits, may increase health-related quality of life (HRQoL) and reduce healthcare costs [10]. Systematic reviews suggest ultra-hypofractionation is associated with similar survival outcomes, compared with standard fractionation [11–14]. However, included studies mainly investigated older patients and patients with unfavorable characteristics [4–6,15,16]. Evidence in more favorable groups is limited.

In 2014, Omuro et al. conducted a single-arm phase II trial in adults with newly diagnosed glioblastoma and a tumor volume $\leq$ 60cc [17]. Patients received a 6-fraction ultra-hypofractionated radiotherapy schedule combined with concurrent and adjuvant temozolomide and bevacizumab. In this study, the median OS was 19 months with a 1-year survival rate of 93%. Despite its limited single-arm phase II design and small sample size (n=40), these results were promising [17]. The current phase III trial aims to evaluate this ultra-hypofractionated regimen (without prophylactic bevacizumab) in a randomized setting and in a broader, real-world glioblastoma population.

Ultra-hypofractionation theoretically increases the risk of late normal tissue toxicity, particularly in organs with a low α/β ratio, such as the brain [18]. In the study by Omuro et al, only 5 patients (12.5%) experienced grade 3-5 toxicities, which did not exceed the severe toxicity rates reported in the EORTC/NCIC trial [17]. Systematic reviews indicate that both conventional and ultra-hypofractionated therapy were generally well tolerated and that toxicity was comparable, with mostly mild acute adverse effects [11–14].

The *Glioblastoma: Optimizing Logistics and Dose* (GOLD) study was initiated to investigate whether an ultra-hypofractionated radiotherapy schedule of 6 fractions of 6 Gy over two weeks, is non-inferior to the standard 30x2Gy schedule, in terms of survival and toxicity. The study also evaluates whether this ultra-hypofractionated schedule provides comparable HRQoL, while reducing treatment costs. These predefined secondary outcomes will be reported separately. Here, we report OS, progression free survival (PFS), and toxicity.

Methods

Study design and patients

This open-label, multicenter, randomized clinical trial was designed to evaluate non-inferiority of ultra-hypofractionated temozolomide-chemoradiation, when compared to standard-fractionation, in glioblastoma patients. The trial was conducted in eight radiotherapy centers in The Netherlands.

Eligible patients were adults with a newly diagnosed histologically confirmed glioblastoma, according to WHO 2016 criteria, after biopsy or resection and a Karnofsky Performance Status (KPS) $\geq$ 70[19,20]. Full eligibility criteria are provided in supplementary material(S1).

Randomization

Patients were randomized 1:1 between two treatment groups, stratified by MGMT promoter methylation status (methylated/unmethylated/unknown), age ($\leq$ 70 vs $>$ 70 years), prior surgical procedure (biopsy/resection) and treatment center. A computer-based randomization tool ensured allocation concealment, with the treatment assignment revealed after patient enrollment.

Treatment

Radiotherapy planning and delivery were performed in all participating centers according to a predefined treatment protocol, including standardized target volume definitions, treatment planning requirements and organ-at-risk dose constraints. The treatment protocol can be found in the supplementary material (S2). Modern radiotherapy techniques were used, including at least intensity-modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT). Dose constraints for organs at risk were adapted for the experimental arm using radiobiological dose conversion with an α/β-ratio of 2 Gy for late responding normal tissues.

In line with the previous phase II trial, patients in the experimental arm received ultra-hypofractionated radiotherapy using a simultaneous integrated boost-like schedule: 6 fractions of 6 Gy to the CTV_{36Gy} (= GTV + 5mm margin) and 6 fractions of 4 Gy to the CTV_{24Gy} (GTV + 15mm margin), three fractions per week during 2 weeks [17]. Thus, the outer CTV region between 5 and 15 mm from the GTV received 6 x 4 Gy rather than 6 x 6 Gy. GTV is defined as the contrast-enhancing lesion, including the resection cavity, on the contrast-enhanced T1-weighted post-operative MRI. An example dose distribution of this regimen is shown in Fig. 1. Patients in the control arm received standard of care radiotherapy in 6 weeks, which consisted of 30 fractions of 2 Gy to the CTV (= GTV + 15mm margin), 5 fractions per week during 6 weeks.

Both treatment regimens included daily concurrent temozolomide chemotherapy; for two weeks in the experimental arm and for six weeks in the control arm. Both arms received up to 6 cycles of adjuvant temozolomide. Concomitant use of dexamethasone and anticonvulsive medication was allowed. As more recent studies did not show a survival benefit of bevacizumab in the treatment of glioblastoma, this drug was omitted in the current study [21–23].

Sample size

The sample size calculation assumed 2-year mortality rates of 73% and 66% in the control and experimental groups, respectively. The anticipated HR specified the treatment effect under the alternative hypothesis, whereas the expected event rates were used to translate the required number of deaths into a total sample size. With an anticipated HR of 0.90, a non-inferiority margin of 1.20, a one-sided α of 0.05, and 80% power, approximately 299 deaths were required. Assuming equal allocation and an average 2-year event proportion of 69.5%, this corresponded to 430 patients. Allowing for 10% attrition, the planned sample size was 474 patients, with 237 per group. Further details are provided in Supplementary Material S3.

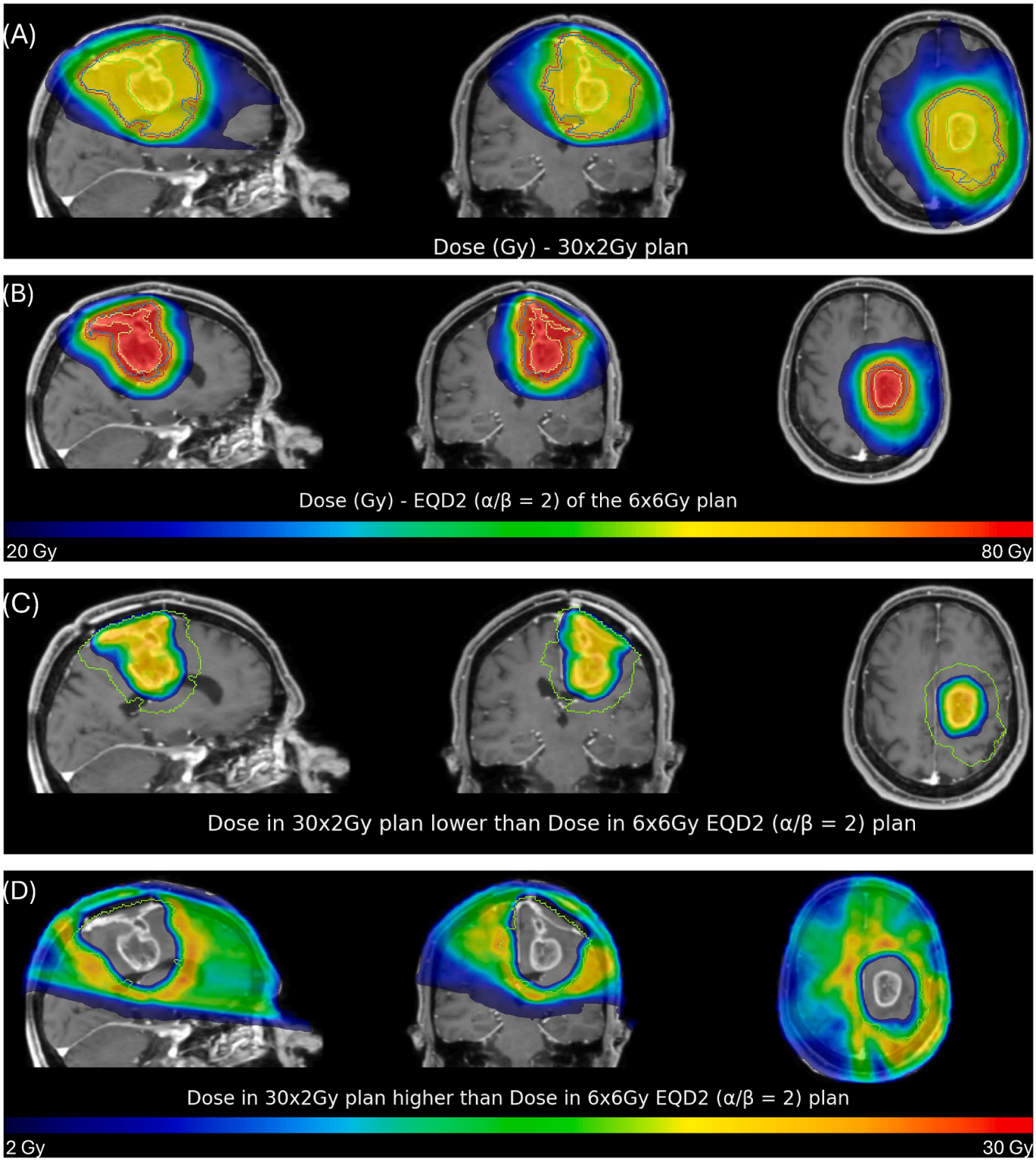

Fig. 1. Radiotherapy dose distributions in a patient planned with both the experimental setup (6x6Gy) and the control arm (30x2Gy) . *Sagittal, coronal, and axial T1Gd MRI slices showing example dose distributions for a patient planned with standard of care (30x2Gy, panel A) and hypofractionated radiotherapy (6x6 Gy, panel B). The 6x6Gy plan was converted to equivalent dose in 2 Gy fractions (EQD2) with $\alpha/\beta = 2$. Dose above 20 Gy is not shown for clarity. GTV (identical for both plans), CTV (30x2Gy: GTV + 15 mm vs 6x6Gy: GTV + 5 mm) and PTV (CTV + 2 mm vs CTV + 2 mm) overlaid in yellow, blue and red colors, respectively. To compare the two plans, regions where EQD2 of the 6x6Gy plan (panel C) or the 30x2Gy plan (panel D) has higher local dose is shown. The outline in green color is the PTV of the 30x2Gy plan, in both panel C and D. Dose differences between −2 and −2 Gy are not shown for clarity. The patient was originally randomized into the experimental arm, therefore the 30x2Gy plan is hypothetical.* Alt text: Dose distributions of two radiotherapy plans (30x2Gy *vs* 6x6Gy) are compared on sagittal, coronal and axial MRI slices. The figure highlights differences in target volumes and regions, and illustrates that the hypofractionated plan uses smaller margins and shows spatial dose differences to the standard plan. The 6x6Gy plan delivers a higher local dose in the GTV than the 30x2Gy plan, but a lower dose in the CTV.

Outcomes

The primary outcome of the GOLD trial was OS, defined as the time from the first day of radiotherapy until death from any cause, with a planned follow-up duration of 24 months. For patients who did not start radiotherapy, the planned radiotherapy start date was used as time origin. Secondary outcomes included radiation-induced toxicity, PFS, and the use of treatment for radiotherapy-induced edema/necrosis (both dexamethasone and bevacizumab).

PFS was defined as the time from the first day of radiotherapy until MRI-confirmed tumor recurrence or death from any cause, Follow-up MRI was performed according to local clinical practice at the participating centers; the imaging schedule was not predefined in the study protocol and could differ between treatment centers. Imaging findings were considered progression only after the confirmation from a multidisciplinary tumor board—supported by a dedicated neuroradiologist's assessment—to distinguish recurrence from pseudoprogression or radionecrosis. If subsequent histology confirmed progression, the date of progression was defined by the first MRI demonstrating progression; conversely, subsequent (histologic) evidence of pseudoprogression or radiation necrosis rather than tumor progression could undo the progression diagnosis. In patients, without a registered progression date, who died with clinical deterioration, the date of death was used as the progression date.

Radiation-induced toxicity was graded according to the Common Terminology Criteria for Adverse Events (CT-CAE) version 5.0[24]. The most objective toxicity terms were evaluated at 1, 3 and 6 months after the end of radiotherapy, such as treatment effects on MRI and seizures. Treatment-induced effects include both pseudoprogression and radiation necrosis. For the purpose of this study, these entities were operationally defined based on timing after radiotherapy. At end of study follow-up, reported radiation necrosis was evaluated based on patient files. In line with national guidelines, this diagnosis was established using multiple sources: radiology reports (in which the Response Assessment in Neuro-Oncology (RANO) criteria were used), multidisciplinary tumor board consensus, followed by PET imaging or histopathology. A central imaging review is ongoing and will be reported separately.

Toxicity outcomes were analyzed only in patients who did not experience progression by that time, and were analyzed separately for the RT period (until 28 days after the last fraction) and the post-RT period (day 29 after last fraction until 2 years follow-up/progressive disease/death from any cause) separately.

HRQoL and cost-effectiveness were also part of the study; these outcomes will be analyzed and reported separately.

Statistics

All statistical analyses were conducted with SPSS Statistics, version 31.0.0.0 (IBM).

OS and PFS were analyzed with Kaplan-Meier estimates. Follow-up for the present analysis was administratively censored at 24 months. Median follow-up was estimated using the reverse Kaplan-Meier method. For the primary analysis of OS, the null hypothesis was that the hazard ratio (HR) for death with ultra-hypofractionated versus standard chemoradiation was at least 1.20 (H_0: HR $\geq$1.20), whereas the alternative hypothesis was that the HR was below 1.20 (H_1: HR <1.20). The prespecified primary analysis used a one-sided non-inferiority log-rank test (α=0.05). Under the proportional-hazards assumption, non-inferiority would be established if the one-sided 95% upper confidence limit for the HR was below 1.20.

Cox proportional hazards models were used to estimate HRs with conventional two-sided 95% CIs for descriptive reporting. The proportional-hazards assumption was assessed using a treatment-by-log (time) interaction. Because hazards were non-proportional, a single overall HR was not considered meaningful for assessing non-inferiority. Treatment effects were therefore explored descriptively using a post-hoc time-dependent Cox model with a treatment-by-period interaction and a 6-month split selected based on the observed survival-curve pattern. These period-specific HRs did not constitute a new formal non-inferiority analysis.

The protocol specified a non-inferiority analysis for PFS. Because of premature trial closure and non-proportional hazards, PFS was analyzed descriptively using a time-varying treatment effect.

Analyses were performed in both intention-to-treat and per-protocol populations. The intention-to-treat population was used for the primary analysis, with the per-protocol analysis serving as a sensitivity analysis.

Toxicity rates were compared between arms with use of a Fisher's Exact test, and relative risks (RR) with 95% CI. Time-to-toxicity was also analyzed with Kaplan-Meier estimates and Cox proportional Hazards models.

Missing data were assumed to be missing at random. Given the high completeness of data ($\geq$95 % for all key variables), analyses were conducted without imputation.

Post-hoc exploratory analyses included a multivariable time-dependent Cox model adjusting for age, KPS, MGMT status and extent of resection, as well as subgroup analyses based on stratification variables.

Results

From November 5, 2020, until the last inclusion of the study at March 25, 2024, 135 patients were enrolled in eight radiotherapy centers in the Netherlands (Fig. 2, Supplementary Table 1). Patient inclusion was stopped after the funding body discontinued support due to slow accrual. Follow-up was administratively censored at 24 months, and the median follow-up was 24 months. All randomized patients were included in the ITT analyses. Two patients had a baseline KPS of 60 and were included as protocol deviations; in both patients, the reduced KPS was attributable to hemiparesis.

Baseline characteristics are shown in Table 1, and were well-balanced between groups.

All patients who started radiotherapy completed the assigned radiotherapy regimen. Two patients in the control arm experienced a temporary interruption of radiotherapy, due to hospitalization and headache.

In the experimental arm, every patient completed the concurrent temozolomide treatment, versus 91% (58/64) in the control arm (Supplementary Table 2). Median cumulative temozolomide dose was 900 mg/m2 in the experimental arm, versus 3000 mg/m2 in the control arm. Adjuvant temozolomide was completed by 65% (42/65) and 70% (45/64), respectively.

After a median follow-up of 24 months, 56 patients (84%) in the experimental group and 36 (53%) in the control group had died. Median OS in the experimental arm was 13.0 months (95% CI 10.3–15.7) and 21.0 months (95% CI not estimable) in the control arm (log-rank test $p < 0.001$; Fig. 3A), with a 1-year survival rate of 52.2% and 70.6%, respectively. The Cox proportional hazards assumption was violated. In a time-dependent Cox model, experimental arm showed an increased risk of death beyond 6 months (HR 2.54, 95% CI 1.57-4.09, $p < 0.001$, Supplementary Table 3). Per protocol analyses yielded consistent results ($\geq$6m: HR 2.48 95% CI 1.54–4.00, $p < 0.001$).

At a median follow-up time of 24 months, 60 (90%) patients in the experimental arm and 51 (75%) patients in the control arm either died or had progression. Median PFS was 9.0 months (95% CI 6.8–11.2) in the experimental arm and 10 months (95% CI 6.8–13.2) in the control-arm (log-rank $p = 0.060$, Fig. 3B) The cox proportional hazards assumption was violated for PFS. In a time-dependent Cox model, the risk of progression or death did not differ clearly during the first 6 months, but was higher in the experimental group thereafter (HR 2.08, 95% CI 1.28-3.38, $p = 0.003$). Per protocol analyses yielded consistent results ($\geq$6m HR 2.01, 95% CI 1.24-3.27, $p = 0.005$).

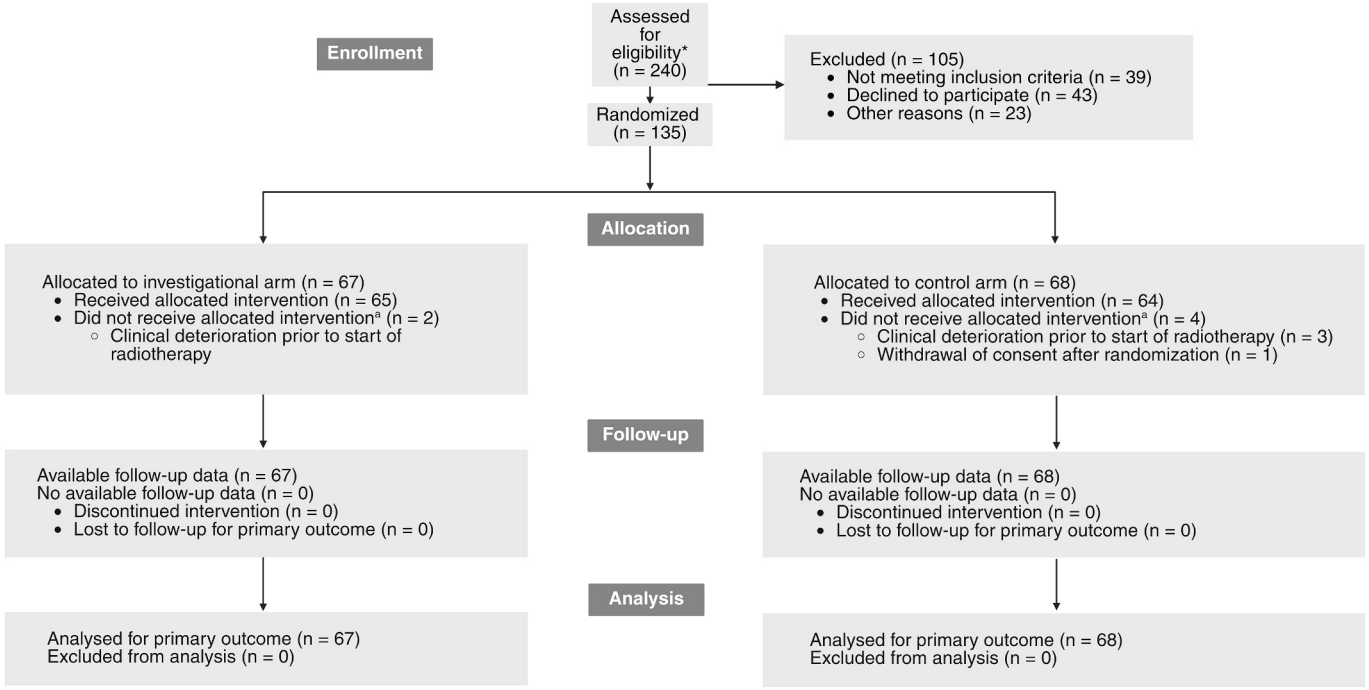

Fig. 2. CONSORT 2025 Flowchart of the GOLD trial. **For four centers, no screening numbers were available. These centers included 27 patients, representing 20 % of the data, therefore n = 240 is an underestimation. [a]Patients that did not receive the allocated intervention were included in the ITT analysis.* Alt text: Flowchart summarizing patient screening, enrollment, randomization, treatment allocation and analysis populations in the GOLD trial. 240 patients were assessed for eligibility (screening numbers were missing for four centers). 105 patients were not included, because they did not meet the inclusion criteria (n=39), they declined to participate (n=43) or because of other reasons (n=23). 67 patients were allocated to the investigational arm, where 65 patients received the allocated intervention, and two patients did not receive the intervention due to clinical deterioration prior to start of radiotherapy. 68 patients were allocated to the control arm, where 64 patients received the allocated intervention, and four did not: three due to clinical deterioration prior to start of radiotherapy and one due to withdrawal of consent after randomization. All patients had available follow-up data and all were included in the analysis for the primary outcome.

Table 1
Baseline characteristics.

Characteristic	Experimental arm (6x6Gy) n = 67	Control arm (30x2Gy) n = 68
Sex: male, n (%)	41 (61%)	46 (68%)
Age at diagnosis, median [IQR]	61 [55– 66]	62 [56 – 67]
T1-CE Tumor lateralization		
Left hemisphere, n (%)	31 (46%)	34 (50%)
Right hemisphere, n (%)	35 (52%)	34 (50%)
Bilateral, n (%)	1 (2%)	0 (0%)
Surgical procedure		
Biopsy, n (%)	7 (10%)	5 (7%)
Debulking, n (%)	41 (61%)	44 (65%)
Macroscopic Total Resection, n (%)	19 (28%)	19 (28%)
IDH mutation		
Wild type, n (%)	66 (99%)	66 (97%)
Mutated, n (%)	1 (2%)	2 (3%)
MGMT methylation		
Unmethylated, n (%)	25 (37%)	28 (41%)
Methylated, n (%)	16 (24%)	16 (24%)
Unknown, n (%)	26 (39%)	24 (35%)
CDKN2A/B homozygous deletion		
Present, n (%)	20 (30%)	22 (32%)
Absent, n (%)	16 (24%)	19 (28%)
Unknown, n (%)	31 (46%)	27 (40%)
KPS at baseline < 80, n (%)	11 (16%)	5 (7%)
Dexamethasone use at baseline		
No use of dexamethasone, n (%)	46 (69%)	49 (72%)
Low dose (≤ 4 mg daily), n (%)	18 (27%)	17 (25%)
High dose (> 4 mg daily), n (%)	3 (5%)	2 (3%)
GTV in cc, median [IQR]*	25.13 [15.35 – 33.06]	21.34 [10.31 – 32.53]

Abbreviations: CDKN2A/B = cyclin-dependent kinase inhibitor 2A/B, GTV = Gross Tumor Volume, IDH = isocitrate dehydrogenase, IQR = Interquartile range, KPS = Karnofsky Performance Score, MGMT = O6-methylguanine-DNA methyltransferase, n = total number of patients.

* GTV's were missing for the 6 patients that were drop-outs, as there was no radiotherapy administered.

Toxicity data at 1, 3 and 6 months after the end of radiotherapy are shown in Supplementary Tables 3-6. The number of patients evaluable for toxicity decreased over time due to death, disease progression or missing clinical/MRI assessments. No grade 4-5 toxicities were observed and most events were grade 1 or 2 in severity (Supplementary Tables 5-7).

Radiation necrosis or pseudoprogression was reported in 32/67 patients (47.8%) in the experimental arm and 11/68 patients (16.2%) in the control arm (Supplementary Table 8). Median time to occurrence was 13.0 months in the experimental arm (95% CI 9.0–17.0), and was not reached in the control arm ($p < 0.001$), with a 1-year cumulative probability of 48% (95% CI 33.1-62.9%) versus 19% (95% CI 6.7–31.3%), respectively (Fig. 4). Risk of radiation necrosis was higher in the experimental arm (HR 5.20, 95% CI 2.56–10.58, $p < 0.001$). Additional competing risk analysis, accounting for earlier progression in the experimental arm, confirmed a higher cumulative incidence of radiation necrosis.

Post-radiotherapy use of dexamethasone and bevacizumab was higher in the experimental arm. Bevacizumab was administered at any timepoint in 21/62 patients (34%) versus 5/61 (8%) in the control arm ($p < 0.001$). Dexamethasone use was also more frequent at 6–12 months in the experimental arm (60–63% vs 31–32%, $p \leq 0.006$; Supplementary Table 9), while baseline and later timepoints showed no significant difference.

Ancillary analyses, including explanatory multivariable and subgroup analyses, confirmed the unfavorable outcomes in the ultra-hypofractionated group. Possibly, this unfavorable effect was more pronounced in patients ≤ 70 years than in those over 60 (Fig. 5, and S5).

Among patients with documented tumor progression, 24 of 54 patients (44.4%) in the experimental arm and 18 of 50 patients (36.0%) in the control arm received second line treatment during follow-up.

Discussion

In this randomized clinical trial, comparing a ultra-hypofractionated radiotherapy schedule (6x6Gy) with the standard treatment schedule (30x2Gy) in patients who underwent temozolomide-chemoradiation for a newly diagnosed glioblastoma, non-inferiority of the experimental regimen was not established. The experimental treatment regimen was associated with an inferior overall survival, inferior progression free survival, and higher toxicity rates.

The schedule used in this study was based on the phase II study by Omuro et al, in which a similar regimen was combined with bevacizumab [17]. They reported a median OS of 19 months, while our study found a median OS of 13 months. These differences likely reflect patient selection by stricter eligibility criteria, including a maximum tumor volume of 60 cc and 125 cc, respectively. Notably, the absence of a control arm in the phase II study limits the generalizability of their

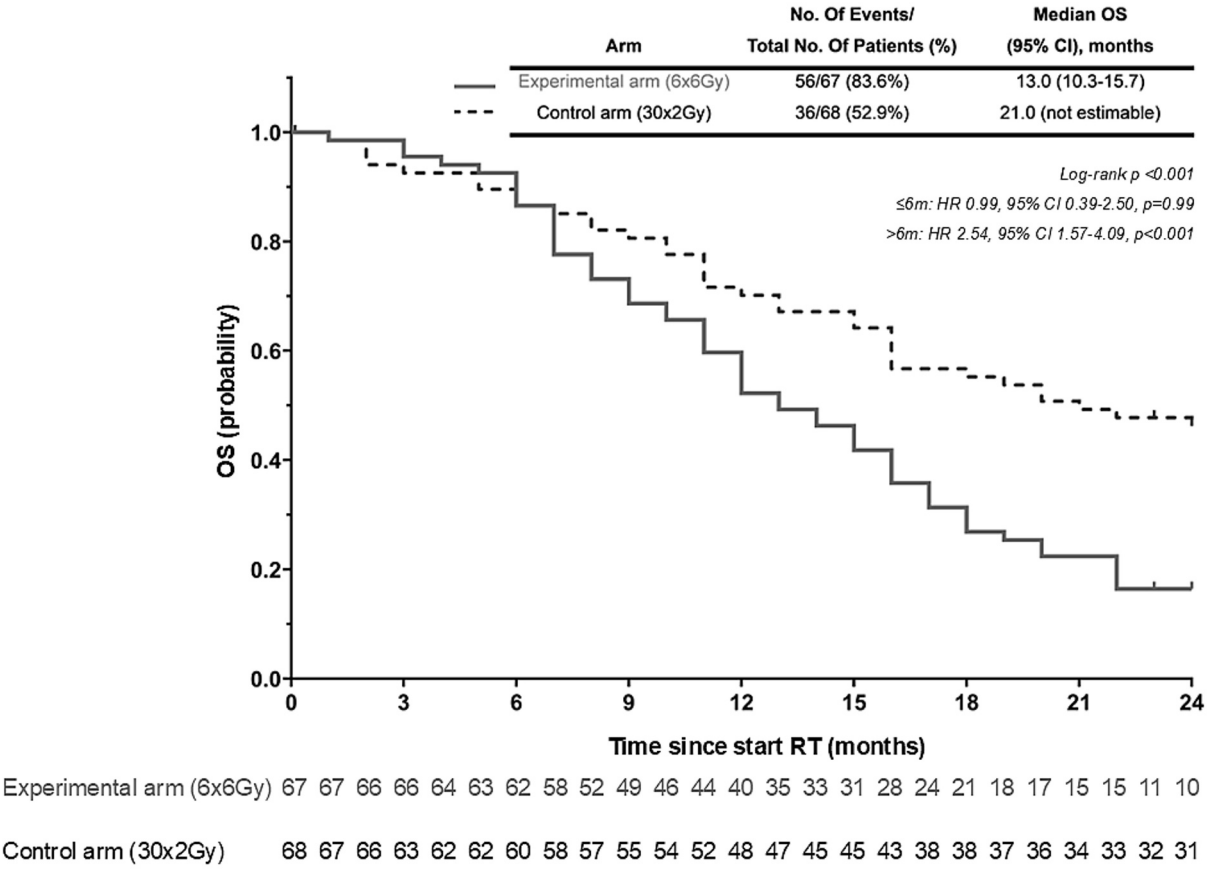

Fig. 3. Overall survival and progression free survival. *Abbreviations: OS = Overall Survival, PFS = Progression Free Survival, RT = Radiotherapy, No. = Number.* Alt text: This figure shows two Kaplan-Meier curves, comparing overall survival and progression-free survival between the experimental and control arms. The figures include crossing curves at 6 months, a number of risk table, and a table with survival analysis data. The upper panel shows overall survival: 56/67 (83.6 %) had an event in the experimental arm, versus 36/68 (52.9 %) in the control arm. The median overall survival was 13 months (95 % CI 10.3–15.7) versus 21 months (CI not estimable), log-rank p <0.001. The time dependent cox-regression analysis showed an HR of 0.99 (95 % CI 0.39–2.50, p=0.99) up to 6 months, versus an HR of 2.54 (95 % CI 1.57–4.09, p<0.001) after 6 months. The figure in the lower panel shows progression-free survival: 60/67 (89.6 %) had an event in the experimental arm, versus 51/68 (75.0 %) in the control arm. The median progression-free survival was 9 months (95 % CI 6.8–11.2) versus 10 months (CI 6.8–13.2), log-rank p = 0.006. The time dependent cox-regression analysis showed an HR of 0.759 (95 % CI 0.40–1.39, p=0.358) up to 6 months, versus an HR of 2.08 (95 % CI 1.24–3.27, p=0.005) after 6 months.

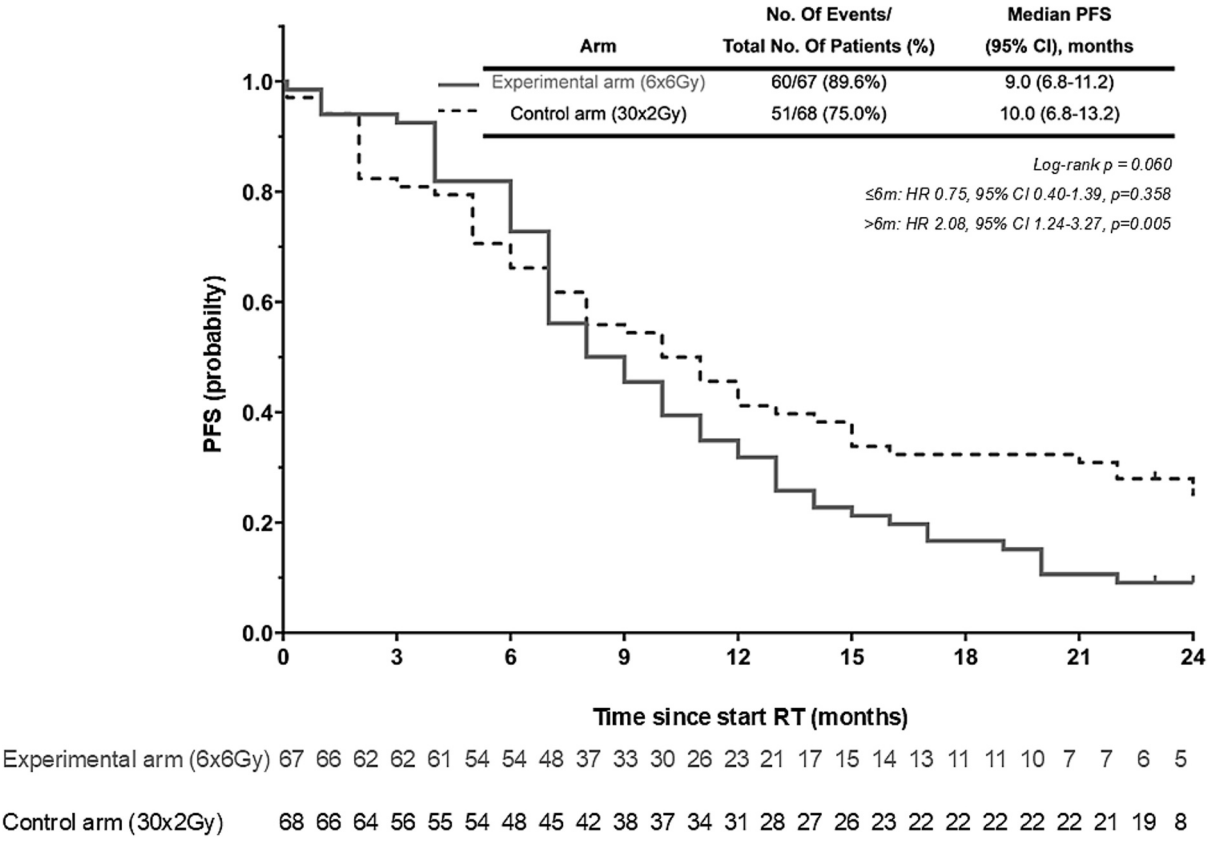

Fig. 3. (*continued*).

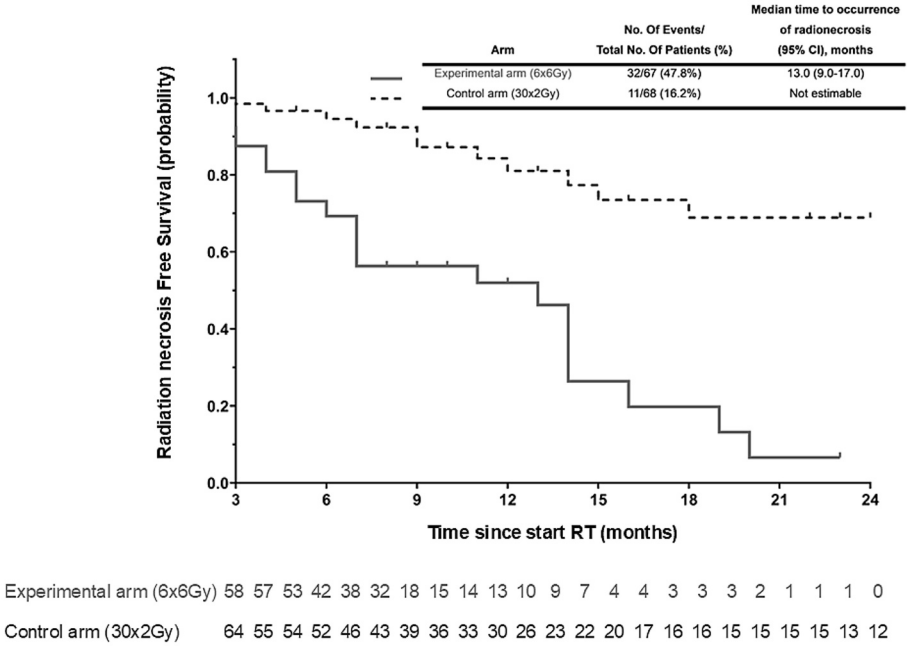

Fig. 4. Time to occurrence radiation necrosis. *Abbreviations: RT = Radiotherapy, No. = Number.* Alt text: Kaplan-Meier curve showing the occurrence of radiation necrosis over time for the two treatment arms. The curves do not cross. The figure also includes data of survival analysis: 32/67 (47.8 %) had an event in the experimental arm, versus 11/68 (16.2 %) in the control arm. The median time to occurrence of radiation necrosis was 13 months (95 % CI 9.0–17.0) and was not reached in the control arm. Below the figure is a number at risk table.

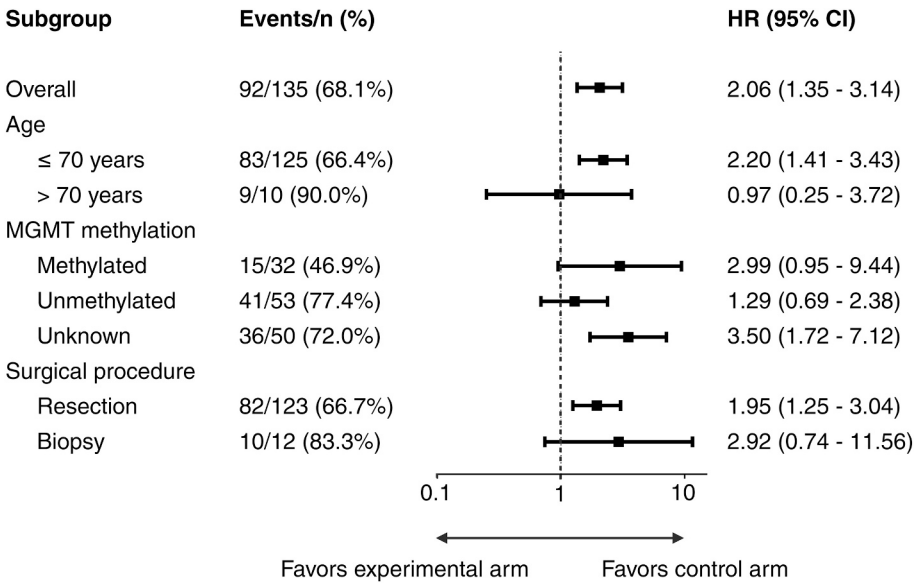

Fig. 5. Subgroup analysis of experimental treatment on overall survival. *Exploratory subgroup analyses of overall survival. Hazard Ratios (HR's) and 95 % Confidence intervals (CI's) were estimated using univariable Cox proportional hazards models within each subgroup. HR > 1 indicates worse survival with experimental treatment compared with standard treatment. Subgroup analyses were exploratory and not adjusted for multiple testing and/or interaction effects. MGMT = O6-methylguanine DNA methyltransferase.* Alt text: Forest plot which shows the number of events, hazard ratios and confidence intervals for overall survival across predefined subgroups. In the middle of the figure is the forest plot, showing the HR and confidence interval with the direction of favoring the experimental or the control arm. In the overall study group, 92/135 (68.1 %) had an event within study duration (HR 2.06, 95 % CI 1.35–3.14). For ages 70 and younger, the number of events was 83/125 (66.4 %) (HR 2.20, 95 % CI 1.41–3.43) and for ages of 71 and above, the number of events was 9/10 (90 %) (HR 0.97, 95 % CI 0.25–3.72). For MGMT methylated patients, the number of events was 15/32 (46.9 %) (HR 2.99, 95 % CI 0.95–9.44), for MGMT unmethylated patients, the number of events was 41/53 (77.4 %) (HR 1.29, 95 % CI 0.69–2.38) and for MGMT unknown, the number of events was 36/50 (72.0 %) (HR 3.50, 95 % CI 1.72–7.12). For patients that underwent a resection, the number of events was 82/123 (66.7 %) (HR 1.95, 95 % CI 1.25–3.04) and for patients that underwent biopsy, the number of events was 10/12 (83.3 %) (HR 2.92, 95 % CI 0.74–11.56).

findings. Survival in our control arm is consistent with outcomes in contemporary glioblastoma trials (mOS 21 months), supporting that our cohort represents a typical trial population [2,21]. Furthermore, we did not combine the ultra-hypofractionated regimen with bevacizumab, but observed higher rates of radiation necrosis and an increase in dexamethasone use. This supports the use of bevacizumab as a treatment for radiation-induced toxicity. However, direct conclusions about the added value of bevacizumab cannot be made.

A larger phase III study, by Perry et al, showed improved survival and limited toxicity in elderly patients receiving hypofractionated temozolomide-chemoradiation (40 Gy in 15 fractions), as compared to hypofractionated radiotherapy alone [4]. The study established this regimen as the standard treatment for elderly and frail patients, but did not include a comparison with standard-fractionated chemoradiation, despite a lower total radiation dose over a longer treatment period. Whether this hypofractionation schedule is non-inferior to regular 30x2Gy-fractionation, remains to be determined (https://clinicaltrials.gov/study/NCT05439278). Like this trial, most evidence on ultra-hypofractionation versus standard fractionation is derived from elderly and poor prognosis patients, in which outcomes appear comparable [4–9,11–15]. However, these results cannot be directly extrapolated to younger, less frail patients. In this context, our trial suggests that ultra-hypofractionation may not be equivalent to standard fractionation in first line treatment and may, in fact, be harmful in standard-risk glioblastoma patients. Notably, our exploratory post-hoc subgroup analysis suggests that the unfavorable effect of the regimen used in our study may be more pronounced in MGMT-methylated patients, and in patients younger than 70 years.

The patients in the experimental arm received a ultra-hypofractionated, simultaneous integrated boost-like radiotherapy schedule of 6 fractions of 6 Gy to the GTV + 5 mm margin, and 6 fractions of 4 Gy to the surrounding CTV (GTV + 15mm margin).The high-dose region (6×6 Gy) corresponds to an EQD2 of 72 Gy for late-responding brain tissue (α/β=2Gy), exceeding the 60 Gy standard regimen and providing a biologically plausible explanation for the increased risk of treatment-related imaging changes. In contrast, the elective CTV dose (6×4 Gy) corresponds to 36 Gy EQD2, substantially below 60 Gy, indicating a lower risk of normal tissue toxicity, but potentially reduced tumor control in this region prone to microscopic disease. Although the shorter overall treatment time may partially compensate for tumor repopulation, even with reasonable time-correction assumptions the CTV dose does not reach biological equivalence with 60 Gy. This imbalance between intensified central dosing and reduced elective dose may explain the observed pattern of necrosis within the GTV and recurrences in the surrounding margin. Additional analyses of the spatial patterns of progression and radiation necrosis – in relation to the CTV/GTV – are planned.

Median cumulative concurrent temozolomide exposure was lower in the experimental arm (900 mg/m2 vs 3000 mg/m2), reflecting the shorter duration of radiotherapy. However, temozolomide administered during the concurrent phase is generally considered to act primarily as a radiosensitizer [25]. Nevertheless, the lower cumulative concurrent exposure may have contributed to the observed survival difference, although it is unlikely to explain the magnitude and time-dependent pattern of this difference on its own [25]

The ultra-hypofractionated treatment schedule in this study was associated with higher toxicity rates, mainly consisting of higher rates of radiation necrosis or pseudoprogression (HR 5.20, 95% CI 2.56–10.58, $p < 0.001$). This may have further complicated the radiologic assessment of tumor recurrence and its challenging distinction with radiation necrosis [26,27]. Misclassification of tumor recurrence as radiation necrosis could, in theory, have led to unjustified termination of anti-tumor-treatment in the intervention arm, potentially contributing to worse overall survival. However, standard clinical procedures were applied and rates of second-line treatment were comparable between treatment arms, making systematic undertreatment in the experimental arm

unlikely [28,29].

Key strengths of the current study include its randomized design, the broad inclusion criteria (reflecting the spectrum of glioblastoma patients undergoing chemoradiation in current clinical practice), prospective collection of toxicity and health-related quality-of-life data (to be published), relatively long follow-up, and the high completeness of the dataset.

Several limitations should be acknowledged. The study began during the COVID-19 pandemic, which caused logistical delays and initial slow accrual. Patient enrollment was further limited by concurrent trials and other practical and clinical factors. Consequently, funding was discontinued, resulting in early trial termination and a smaller sample size with reduced statistical power.

The non-inferiority design assumed proportional hazards, but the observed hazards were non-proportional, precluding meaningful interpretation of the prespecified HR margin of 1.20 over the full follow-up period. The post-hoc time-dependent Cox analysis described the time-varying treatment effect but did not constitute a new formal non-inferiority test. In addition, the anticipated HR of 0.90 favored the experimental arm and reduced the planned sample size compared with an assumption of equal efficacy. The historical event rates were derived from clinically different populations and treatment settings, introducing uncertainty regarding the constancy assumption. Premature trial closure limited power and precision, and subgroup analyses and secondary endpoints should therefore be considered exploratory.

Radiotherapy planning was performed according to a standardized protocol, but no central review of treatment plans was conducted. This may have introduced variability in treatment planning. However, these procedures were in line with our national guidelines, and while the lack of central review forms a limitation, it reflects the pragmatic design of our trial. In addition, MRI frequency and the use of advanced imaging were not mandated and varied according to local clinical practice. Finally, although progression assessments were supported by dedicated neuroradiological review and multidisciplinary confirmation, misclassification of progression, pseudoprogression, and radiation necrosis cannot be excluded. Use of advanced imaging for this distinction was only performed at the discretion of the local treating team. A central imaging review is ongoing.

Although the results of a first interim analysis did not justify termination, the described effects might have led to trial termination, regardless of funding discontinuation. Despite these limitations, the Substantial increase in mortality after 6 months and the consistency of unfavorable findings across survival and toxicity endpoints provide no support for replacing standard chemoradiation with this regimen.

These findings provide randomized evidence against adoption of an attractive, but unproven accelerated strategy, in this difficult-to-treat cancer. They do not support the use of the 6x6Gy regimen as a substitute for standard treatment. Future studies on ultra-hypofractionated first-line glioma treatment, (a) should study optimal schedules for efficacy in early-phase clinical studies, (b) may benefit from strategies to reduce clinically relevant radiation necrosis, such as the prophylactic or early symptomatic use of bevacizumab, as explored in the ongoing BRAINS study,[30]and (c) may use MR-guided, adaptive treatment planning to obtain a better balance between optimal tumor control and minimal healthy tissue damage.

In conclusion, non-inferiority of the ultra-hypofractionated radiotherapy schedule of 6x6Gy, when compared with a standard treatment schedule of 30x2Gy, in patients with a newly diagnosed glioblastoma, could not be established. This ultra-hypofractionated scheme resulted in inferior overall survival, inferior progression free-survival and higher rates of reported radiation necrosis/pseudoprogression. Therefore, our study offers no support for this ultra-hypofractionated chemoradiation as a substitute for standard treatment in newly diagnosed glioblastoma.

CRediT authorship contribution statement

Anouk M. de Jong: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Project administration. **Arthur T.J. van der Boog:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Gerda Wester:** Writing – review & editing, Resources, Investigation. **Daniëlle B.P. Eekers:** Writing – review & editing, Resources, Investigation. **Tom C.G. Budiharto:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Tom Rozema:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Frank J. Lagerwaard:** Resources, Methodology, Investigation, Conceptualization. **Anna M.E. Bruynzeel:** . **Crystal de Groot:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Matthijs van der Meulen:** Writing – review & editing, Resources, Investigation. **Fia Cialdella:** Writing – review & editing, Resources, Investigation. **Jan-Willem Dankbaar:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jeroen Hendrikse:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Karin E. Kleynen:** Writing – review & editing, Resources, Investigation. **An Claes:** Writing – review & editing, Resources, Investigation. **Mariëlle E.P. Philippens:** Writing – review & editing, Supervision, Resources, Project administration, Investigation. **Ernst J. Smid:** Writing – review & editing, Resources, Investigation. **Filip Y.F.L. de Vos:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Peter S.N. van Rossum:** Conceptualization, Methodology, Writing – review & editing. **Pierre A. Robe:** Writing – review & editing, Resources, Investigation. **Szabolcs David:** Writing – review & editing, Supervision, Resources, Investigation, Formal analysis. **Tom J. Snijders:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Joost J.C. Verhoeff:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Ethics

Patients provided written informed consent. The study was approved by the Medical Ethics Review Committee (METC) NedMec (METC 20/104), conducted in accordance with the Declaration of Helsinki and applicable regulations. The study is registered in The Netherlands trial registry (NL72953.041.20). The trial was co-developed in collaboration with the UMC Utrecht Brain Tumor Patient Advisory board. No substantial changes were made to the protocol after study initiation.

Data statement

Upon informed consent, patients are aware that their pseudonymized data may be shared with participating hospitals in favor of conducting the research described in this application. These data will remain property of this project and will only be provided upon request and after quality check at/by the research board of this project.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Joost J.J.C. Verhoeff reports financial support was provided by Netherlands Organisation for Health Research and Development

(ZonMw). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Additional study methods and results, including eligibility criteria, radiotherapy treatment protocol, sample size calculation, adverse event reporting, ancillary analyses, and supplementary tables. Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2026.111726.

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