Dose escalation with intraoperative radiotherapy in newly diagnosed glioblastoma (INTRAGO-II): an open-label, multicentre, randomised, controlled, phase 3 trial

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Summary

Background Despite maximal safe resection and chemoradiotherapy, most glioblastomas recur locally. We aimed to evaluate whether additional intraoperative radiotherapy compared with standard of care improves outcomes in patients with newly diagnosed glioblastoma.

Methods INTRAGO-II was an open-label, multicentre, randomised, controlled, phase 3 trial enrolling patients aged 18–80 years with supratentorial glioblastoma amenable to resection of the contrast enhancing tumour with Karnofsky performance score (KPS) of ≥60%. Patients from 18 centres in Brazil, Canada, China, Germany, Spain, South Korea, and the USA were randomly assigned (1:1) intraoperatively to receive additional kilovoltage intraoperative radiotherapy with 30 Gy (intraoperative radiotherapy group) or surgery alone (standard-of-care group), stratified by age, KPS, and residual tumour. Postoperative treatment consisted of external-beam radiotherapy to 60 Gy with concurrent temozolomide (75 mg/m²), followed by six adjuvant cycles of temozolomide (150–200 mg/m², days 1–5 every 28 days). The primary endpoint was median progression-free survival in the full-analysis set, confirmed by masked, centralised review. This ongoing study is closed to recruitment and is registered with ClinicalTrials.gov, NCT02685605.

Findings Between Dec 9, 2016, and June 17, 2024, of 411 patients assessed for eligibility, 314 were randomly assigned. The full-analysis set comprised 298 patients (intraoperative radiotherapy, n=161; standard-of-care, n=137), of whom 127 (43%) patients were female and 171 (57%) were male. Data on race and ethnicity were not collected. At a median follow-up of 17·2 months (IQR 10·5–27·1), median progression-free survival was 11·0 months (95% CI 9·2–12·6) in the intraoperative radiotherapy group versus 11·4 months (9·7–13·9) in the standard-of-care group (hazard ratio [HR] 1·1, 95% CI 0·85–1·44; p=0·47). Local recurrence was the predominant pattern of failure in both groups (76 [72%] in the intraoperative radiotherapy group *vs* 60 [71%] in the standard-of-care group, p=0·87). The most common grade 3–4 adverse events were seizure (21 [13%] in the intraoperative radiotherapy group *vs* nine [7%] in the standard-of-care group), radiation necrosis (11 [7%] *vs* three [2%]; p=0·06), thrombocytopenia (seven [4%] *vs* 11 [8%]), and muscle weakness (12 [7%] *vs* 19 [14%]). In total, 252 serious adverse events occurred in 105 (65%) patients in the intraoperative radiotherapy group and 142 serious adverse events in 72 (53%) patients in the standard-of-care group. Of these, 65 (26%) events in 40 (38%) patients in the intraoperative radiotherapy group and 27 (19%) events in 19 (26%) patients in the standard-of-care group were considered possibly related to the treatment. Of all grade five adverse events reported, 14 in the intraoperative radiotherapy group (CNS toxicity [n=2], myocardial infarction [n=2], sepsis [n=2], and one each cardiac arrest, fever, lung infection, fracture, postoperative haemorrhage, neoplasm, haematoma, and not otherwise specified death) and six in the standard-of-care group (lung infection [n=2], and one each multiorgan failure, encephalitis, neoplasm, and cystitis) were attributable to specific CTCAE terms.

Interpretation Instant, spatially precise dose escalation with intraoperative radiotherapy added to standard of care did not improve outcomes, questioning the value of further local dose intensification in resectable glioblastoma.

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Introduction

Glioblastoma is the most common and most aggressive primary malignant brain tumour in adults, with an overall incidence of 3–5 cases per 100 000 population in Europe and the USA.[1] Despite maximal safe resection followed by postoperative radiotherapy with concomitant and adjuvant temozolomide,[2] prognosis remains dismal, with a median overall survival of approximately 12–18 months and a median progression-free survival of 6–12 months.[3–5] The standard of care has remained

Research in context

Evidence before this study

When we published the phase 1/2 INTRAGO-I trial, we searched for studies in MEDLINE (from Jan 1, 1946), Embase (from Jan 1, 1974), PubMed (from Jan 1, 1996), Cochrane Database of Systematic Reviews (CDSR; from Jan 1, 1995), CENTRAL (from Jan 1, 1996), DARE (from Jan 1, 1994), and the Health Technology Assessment Database (from Jan 1, 1996) to April 8, 2013, using the keywords "intraoperative radiotherapy" OR "IORT" AND "Glioblastoma". The resulting papers were examined manually. No randomised controlled trials were identified. Retrospective studies did not show a consistent signal with the addition of intraoperative radiotherapy. We then conducted the initial phase 1/2 INTRAGO-I trial and found an overall median progression-free survival of 11·2 months with delivery of intraoperative therapy, suggesting a modest benefit. An updated literature search noted an additional, international pooled analysis and meta-analysis reporting favourable outcomes with intraoperative radiotherapy compared to historical controls.

Added value of this study

INTRAGO-II, a large, international, randomised, controlled, phase 3 trial testing the addition of 30 Gy low-kilovolt intraoperative radiotherapy radiation boost in addition to standard-of-care chemoradiotherapy in newly diagnosed, resectable glioblastoma did not provide a progression-free survival or overall survival benefit, nor did it alter local recurrence patterns. The study design was robust, with appropriate performance characteristics to support the reliability of the finding.

Implications of all the available evidence

Findings from this randomised, phase 3 trial indicate that further intensification of local radiation dose, regardless of the applied method, is unlikely to improve outcomes in resectable glioblastoma.

essentially unchanged since 2005, and multiple phase 3 trials of novel systemic treatments have failed to show a meaningful survival benefit.

Most recurrences occur locally within a 2 cm margin of the resection cavity,[6] implicating residual tumour cells and their revascularisation-promoting tumour microenvironment within the peritumoural zone as key drivers of early relapse.[7] Accordingly, a range of approaches to intensify local treatment have been explored, including more extensive surgical resection,[8] local chemotherapy,[9] brachytherapy,[10] and dose-escalated external-beam radiotherapy.[11,12]

Dose-escalated external-beam radiotherapy, however, has been limited by technical (linear accelerator *vs* gamma knife–CyberKnife; intensity modulated radiotherapy *vs* 3D-CRT), temporal (upfront *vs* post-chemoradiotherapy), and spatial (heterogeneous dose distribution, radiotherapy dose limitations owing to proximity to critical structures) challenges. Consequently, no large, randomised trials have yet shown a meaningful clinical benefit with dose escalated radiation boost approaches.[11–13]

Intraoperative radiotherapy represents a technically attractive alternative that delivers immediate, high radiation doses to the resection cavity. The characteristic steep dose gradient of kilovoltage irradiation results in high surface doses with rapid attenuation, effectively confining the radiation boost to the adjacent resection cavity.[14] In addition, low-energy x-rays emitting 50 kV photons at a high dose-rate exhibit a high relative biological effectiveness (1·3–1·5), similar to that of protons (1·1–1·5) and carbon ions (1·5–5·0), which might induce a more complex and spatially clustered DNA damage and thereby a greater biological effect.[15]

The INTRAGO-I phase 1/2 trial previously showed both feasibility and safety of adding intraoperative radiotherapy to the standard of care in newly diagnosed glioblastoma.[16] Data from this study and an international pooled analysis compared favourably with historical controls for progression-free survival, local control, and overall survival, without increased toxicity,[17] supporting further evaluation in a confirmatory trial.

We therefore initiated INTRAGO-II, an international, randomised, phase 3 study designed to establish whether the addition of a 30 Gy radiation boost delivered to the resection cavity using intraoperative radiotherapy, an optimal technique with sharp dose gradient, improves progression-free survival in patients with resectable, newly diagnosed glioblastoma receiving standard of care.

Methods

Study design and participants

INTRAGO-II was an open-label, multicentre, randomised, controlled, phase 3 trial conducted across 18 centres in Brazil (n=1), Canada (n=1), China (n=1), Germany (n=8), Spain (n=2), South Korea (n=1), and the USA (n=4). The trial was approved by the ethics committee of the University of Heidelberg in August, 2015 (approval number 2015-582S-MA) and was reviewed and approved by the German Federal Office for Radiation Protection. The trial protocol was amended on Nov 16, 2017, and Sept 3, 2020, to incorporate evolving standard-of-care treatments following the publication of positive phase 3 trial data: the addition of lomustine (also called CCNU) to temozolomide for *O*-6-methylguanine-DNA methyltransferase (MGMT)-methylated tumours[5] and the

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See Online for appendix

optional use of tumour treating fields[4] were permitted at the discretion of the treating physician. Details on all substantial changes to the protocol, approvals by the ethics committees of all participating institutions, and the initial protocol are provided in the appendix (pp 17–26).

Patients with newly diagnosed glioblastoma were randomly assigned (1:1) to intraoperative radiotherapy and standard-of-care surgery and postoperative chemoradiotherapy or standard of care only. Eligible patients were aged 18–80 years with a Karnofsky performance score (KPS) of 60% or more, exhibited supratentorial T1-Gd enhancing lesions amenable to total resection, with intraoperative feasibility of intraoperative radiotherapy and had adequate organ function. Key exclusion criteria included multicentric disease, previous cranial radiotherapy, recent cytotoxic therapy, substantial competing comorbidity limiting life expectancy, previous antiangiogenic therapy, MRI contraindications, pregnancy or breastfeeding, and intraoperative radiotherapy dose (D_{IORT}) estimation to adjacent organs exceeding 8 Gy where available, but not specifically collected as part of the trial procedures. Written informed consent was obtained from all patients before surgery. Patients were informed about the study design, including intraoperative randomisation, the open-label nature of the trial, and the potential risks and benefits of intraoperative radiotherapy. Patient and public involvement was incorporated through ongoing engagement with the patient organisations yeswecan!cer and the Rhein-Neckar Brain Tumour Support Group, who provided input on study design and patient communication. This study is registered with ClinicalTrials.gov, NCT02685605.

Randomisation and masking

Patients were randomly assigned intraoperatively immediately after tumour resection and haemostasis and estimation of extent of resection, via web-based electronic case report forms, by use of variable block randomisation allocating patients (1:1) to receive either intraoperative radiotherapy or standard of care. Stratified block randomisation was done at site level with block sizes of 4 and 6, with strata: age (<65 *vs* ≥65 years), KPS (90–100% *vs* 60–80%), and anticipated thickness of the residual T1-Gd-enhancing margin (≥0·5 cm or multiple foci *vs* <0·5 cm). Participants, physicians, and investigators were not masked to the assigned treatment. The participants were informed of their allocation on recovery from anaesthesia.

Procedures

All patients needed to undergo maximal safe surgical resection. The decision to proceed with intraoperative radiotherapy was based on the neurosurgeon's intraoperative assessment of having achieved maximal safe resection and adequate haemostasis. In the experimental group, intraoperative radiotherapy was delivered using the INTRABEAM system (Carl Zeiss Meditec AG, Oberkochen, Germany), by use of a spherical applicator sized for a tight cavity fit. The recommended surface dose was 30 Gy, whereas continuous dose reductions to 20 Gy were permitted in case an organ at risk structure would receive more than 8 Gy; dose reductions below 20 Gy were not allowed. Extent of resection was assessed on early postoperative contrast-enhanced T1-weighted MRI (24–72 h). T2–fluid attenuated inversion recovery abnormalities were documented but were not used to define resection completeness, consistent with standard neurosurgical practice at the time of trial design.

Postoperative chemoradiotherapy (in both groups) was initiated 3–5 weeks after surgery. External-beam radiotherapy was applied in 30 fractions of 2 Gy (daily, 5 days per week). Target delineation followed RTOG or European Organisation for Research and Treatment of Cancer/European Society of Therapeutic Radiology and Oncology Advisory Committee in Radiation Oncology Practice (EORTC/ESTRO-ACROP) recommendations.[18,19] In case an organ at risk was in proximity to the resection cavity, the intraoperative radiotherapy dose was converted to equivalent dose in 2 Gy fractions (EQD2; α/β=3; RBE=1·3) in order to meet composite dose constraints (eg, optic apparatus 55 Gy; brainstem 66 Gy EQD2). Concurrent temozolomide was given at 75 mg/m² daily throughout external-beam radiotherapy, with interruptions as clinically indicated. The protocol was amended to allow for the addition of lomustine in accordance with the CeTeG protocol[5] as well as optional use of tumour-treating fields after publication of the EF14 study.[4] Adjuvant chemotherapy with temozolomide commenced 4 weeks after external-beam radiotherapy for six 28-day cycles (days 1–5 at 150–200 mg/m²). Tumour tissue obtained during surgery was processed for histopathological and molecular analysis at each participating centre. The final integrated diagnosis, including isocitrate dehydrogenase 1 and 2 mutation status, was done locally according to institutional standards. *MGMT* promoter methylation status was established locally by use of either methylation-specific PCR or pyrosequencing, depending on institutional practice. No central pathology review was done.

Radiological progression, which constituted the primary component of progression-free survival events, was assessed by quarterly MRIs and centralised imaging review masked to the treatment group according to RANO criteria with study-specific modifications. On first occurrence of radiological progression, a confirmatory MRI scan was scheduled within 4–6 weeks. The masked review evaluated all imaging timepoints necessary for the assessment of the primary endpoint, including baseline postoperative MRI and all subsequent follow-up

scans. Details of the standardised MRI protocol are provided in the imaging charter in the appendix. In brief, each MRI examination included contrast-enhanced T1-weighted, T2/FLAIR, and dynamic susceptibility contrast perfusion sequences. We also incorporated quantitative magnetic resonance perfusion analysis, requiring a relative cerebral blood volume (rCBV) of at least 1 in at least one measurable lesion for a diagnosis of progression, with radiological confirmation on a subsequent scan. New lesions were required to be measurable (≥10×10 mm) to constitute progression. Centralised and masked neuroradiological review ensured consistency of interpretation of progression-free survival in both groups across participating centres and was aimed at improved differentiation between true progression and treatment-related changes such as pseudoprogression or radionecrosis.

Quality of life was evaluated by use of the EORTC QLQ-C30 and QLQ-BN20 questionnaires, and activities of daily living by the Barthel Index, assessed at baseline within 1 week before surgery, during the first week of external-beam radiotherapy, 6 weeks after chemo-radiotherapy, and every 3 months thereafter, even in the event of early progression. Neurological examinations and MRI were obtained at all scheduled follow-up visits, with radionecrosis classified as an event of special interest. Adverse events were systematically recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Data on sex was collected via the physician's report on an electronic case report form. Data on race or ethnicity were not collected as this was not standard or required by the time the trial was planned.

Details on quality assurance and monitoring are provided in the appendix (p 31).

Outcomes

The primary endpoint was median progression-free survival, defined as the time from randomisation to the first occurrence of radiological progression, initiation of new or salvage treatment, unequivocal clinical deterioration attributable to tumour, or death from any cause, consistent with FDA/EMA guidance on progression-free survival endpoints in oncology.

Secondary endpoints included median overall survival, local recurrence defined as progression-free survival within a 1 cm margin around the cavity, and overall survival stratified by site or pattern of failure, residual disease volume, applicator size, age, KPS, and molecular subgroups (eg, MGMT promoter methylation and *IDH1* mutation status), respectively. Additional secondary outcomes included patient-reported quality of life, activities of daily living, and treatment-related neurotoxicity. Results on further secondary endpoints, including quality-of-life assessments and progression-free survival within a 2 cm margin, will be reported separately from the primary analysis.

Statistical analysis

The fixed-design sample size calculation aimed to enrol 314 patients to detect a hazard ratio (HR) of 0·67 (median progression-free survival 13·5 *vs* 9·0 months) with 80·2% power at one-sided α=0·05, assuming a monthly discontinuation rate of 6·5%.

A planned non-binding interim analysis following recruitment of 200 patients was done in May, 2023, to assess safety and exclude imbalances of molecular characteristics between groups (final histology after randomisation). On recommendation by the data safety monitoring board (DSMB), the study was continued without modification thereafter. In October, 2025, the

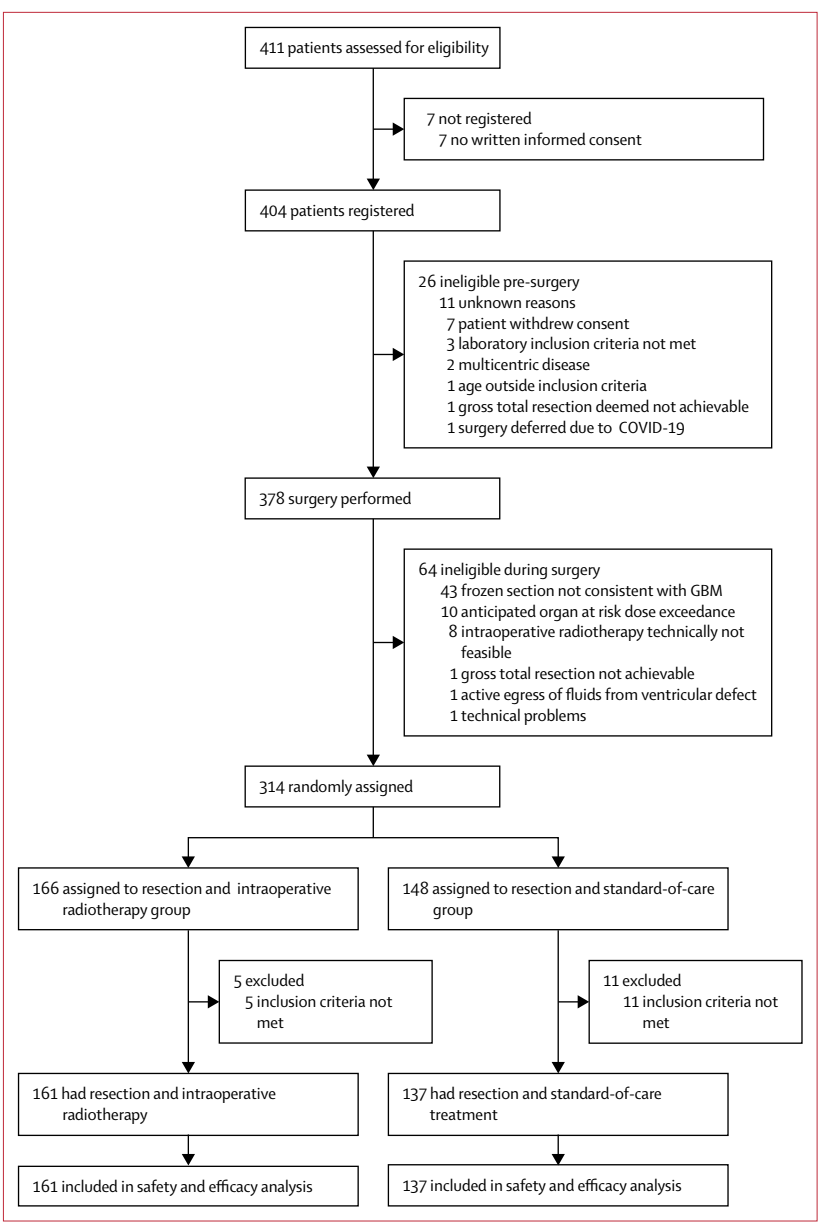


Figure 1: **Trial profile**

DSMB established that a sufficient number of events had occurred for the primary endpoint of progression-free survival to perform an initial analysis with an adequate statistical power to assess differences between the groups. Therefore, a database soft lock was conducted on Oct 6, 2025.

The full-analysis set included all randomly assigned patients analysed by allocated group, with exceptions for those determined to be ineligible post-randomisation (ie, in cases where the final integrated neuropathological diagnosis did not confirm glioblastoma [n=12] or where documentation deficiencies in the informed consent process were identified during routine monitoring [n=4]). All patients who discontinued the trial because of patient or investigator decision contributed to the efficacy analysis up to the date of their last visit (censored at that timepoint) and to the safety analysis for all adverse events documented before withdrawal. The overall rate of grade 3-4 adverse events per patient and the adverse events over time intervals were calculated in a post hoc-approach. Time-to-event outcomes including progression-free survival and overall survival were estimated with Kaplan–Meier methods and compared by use of log-rank tests. Surviving patients without event-defining criteria at last follow-up were censored for progression-free survival on the day of the last follow-up visit. Death was considered a progression-free survival endpoint when occurring no more than 3 months after the last study visit. Patients who had formally discontinued study participation but who died within 3 months of their last study visit were retrospectively reclassified from discontinued to reached progression-free survival endpoint, thereby counting death as a progression-free survival event in the primary analysis. For patients not known to have died, overall survival was censored on the last date known alive. Regular follow-up visits at 3-month intervals were scheduled to maintain patient engagement. Significance was determined by use of a one-sided alpha at 5% for progression-free survival or overall survival (on the basis of the directional hypothesis derived from preceding phase 1/2 data). Differences in categorical variables were assessed by use of Pearson's χ^2 test or Fisher's exact test. Additional sensitivity and subgroup analyses also used the proportional hazard model. For statistical analyses, SAS version 9.4, R and GraphPad Prism 10 (GraphPad Software, Boston, MA, USA) were used. Graphical elements were generated by use of SAS, GraphPad Prism, R. and Adobe Illustrator 2023 (Adobe, San Jose, CA, USA). Data was monitored by a DSMB.

	Intraoperative radiotherapy group (n=161)	Standard-of-care group (n=137)
Sex		
Male	97 (60%)	74 (54%)
Female	64 (40%)	63 (46%)
Age, years	62 (54–68)	63 (56–69)
Karnofsky performance score		
90–100	97 (60%)	83 (61%)
70–80	52 (32%)	43 (31%)
<70	12 (7%)	11 (8%)
Residual tumour*		
Measurable	35/107 (33%)	27/85 (32%)
Not measurable	3/107 (3%)	1/85 (1%)
Not present	69/107 (64%)	57/85 (67%)
Isocitrate dehydrogenase 1		
Wild-type	150 (93%)	128 (93%)†
Mutation	11 (7%)	7 (5%)
O-6-methylguanine-DNA methyltransferase methylation status		
Methylated	64 (40%)	60 (44%)
Unmethylated	85 (53%)	63 (46%)
Unknown	12 (7%)	14 (10%)
Completion of chemoradiotherapy		
Full-analysis set	139/161(86%)	107/137 (78%)
Patients continuing trial to this point	139/148 (94%)	107/115 (93%)
Cycles of adjuvant chemotherapy		
6	123 (76%)	99 (72%)
3–5	14 (9%)	12 (9%)
<3	24 (15%)	26 (19%)
Other or additional first line therapies‡		
Tumour-treating fields	16 (10%)	8 (6%)
Lomustine	16 (10%)	8 (6%)

Data are n (%) or median (IQR). KPS=Karnofsky performance score. *Assessed by early postoperative MRI (24–72 h) in all patients with availability. †Two patients had no data available for isocitrate dehydrogenase 1 mutation status. ‡Following publication of positive trial data for lomustine–temozolomide combination therapy (CeTeG/NOA-0922) and tumour treating fields (EF-145), the protocol was amended to permit the addition of lomustine or tumour-treating fields at the discretion of the treating physician.

Table 1: **Baseline characteristics**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 9, 2016, and June 17, 2024, 411 patients were assessed for eligibility, 404 patients signed informed consent forms and 314 were enrolled and randomly assigned, with 166 (53%) assigned to the experimental group receiving additional intraoperative radiotherapy and 148 (47%) assigned to the standard-of-care group (appendix p 27). A total of 97 patients were excluded before randomisation for various reasons: of the 404 registered patients, seven did not provide informed consent, 26 were identified as ineligible before surgery, primarily for unknown reasons (n=11) or withdrawal of consent (n=7; figure 1), and 64 patients were deemed ineligible during surgery, mostly because frozen tumour sections were not consistent with glioblastoma (n=43), due to anticipated organ at risk dose exceedance (n=10),

or because intraoperative radiotherapy was technically not feasible (n=8; figure 1). After randomisation, 16 patients were excluded owing to lack of confirmed diagnosis (n=12) or invalid informed consent (n=4), resulting in a full-analysis set population of 298 patients (figure 1) originating from Germany (n=198), USA (n=37), Spain (n=33), Canada (n=21), China (n=5), South Korea (n=3), and Brazil (n=1). Of these, 161 (54%) were allocated to the intraoperative radiotherapy group and 137 (46%) to the standard-of-care group.

Baseline patient and tumour characteristics were balanced, including age, Karnofsky performance score, extent of resection, isocitrate dehydrogenase 1 status and MGMT promoter hypermethylation (table 1). The median age was 62 years (IQR 56–69); 127 (43%) patients were female and 171 (57%) were male. Gross total resection was achieved in 69 (64%) of 107 patients in the intraoperative radiotherapy group and 57 (67%) of 85 patients in the standard-of-care group. Both groups showed similar proportions of patients completing chemoradiotherapy (139 [86%] of 161 patients in the intraoperative radiotherapy group *vs* 107 [78%] of 137 patients in the standard-of-care group and the full six cycles of adjuvant chemotherapy (123 [76%] intraoperative radiotherapy group vs 99 [72%] standard-of-care; table 1). 16 (10%) patients in the intraoperative radiotherapy group and eight (6%) patients in the standard-of-care group received tumour-treating fields. In addition, 16 (10%) patients in the intraoperative radiotherapy group and eight (6%) patients in the standard-of-care group received chemotherapy with lomustine as per the CeTeG protocol. Of the 161 patients in the intraoperative radiotherapy group, 115 (71%) received the planned 30 Gy surface dose and 46 (29%) received a reduced dose (range 20–25 Gy) owing to proximity to organs at risk. The median applicator size selected was 30 mm (range 15–45 mm).

The median follow-up was 17·2 months (IQR 10·5–27·1). 47 (16%) participants withdrew from the trial before reaching the study endpoint (19 [12%] in the intraoperative radiotherapy group and 28 [20%] in the standard-of-care group). Three (2%) of patients in the intraoperative radiotherapy group and 14 (10%) in the standard-of-care group discontinued the trial within the first 50 days after surgery, mostly as a result of patient choice (n=30) or loss to follow-up (n=9).

At database lock on Oct 6, 2025, 65 (22%) patients remained alive and at follow-up. There were 129 progression-free survival events in the intraoperative radiotherapy group and 97 in the standard-of-care group. Median progression-free survival was 11·0 months (95% CI 9·2–12·6) in the intraoperative radiotherapy group versus 11·4 months (9·7–13·9) in the standard-of-care group (HR 1·1, 95% CI 0·85–1·44; p=0·47; figure 2A). The progression-free survival endpoint was predominantly reached owing to radiographic progression in both groups (73 [57%] in the intraoperative radiotherapy group and 60 [62%] in the standard-of care group), followed by death (33 [26%] in the intraoperative radiotherapy group *vs* 18 [19%] in the standard-of-care group), initiation of new therapy (12 [9%] in the intraoperative radiotherapy group *vs* 14 [14%] in the standard-of care group; appendix p 15), clinical progression (seven [5%] in the intraoperative radiotherapy group *vs* one [1%] in the standard-of care group), and

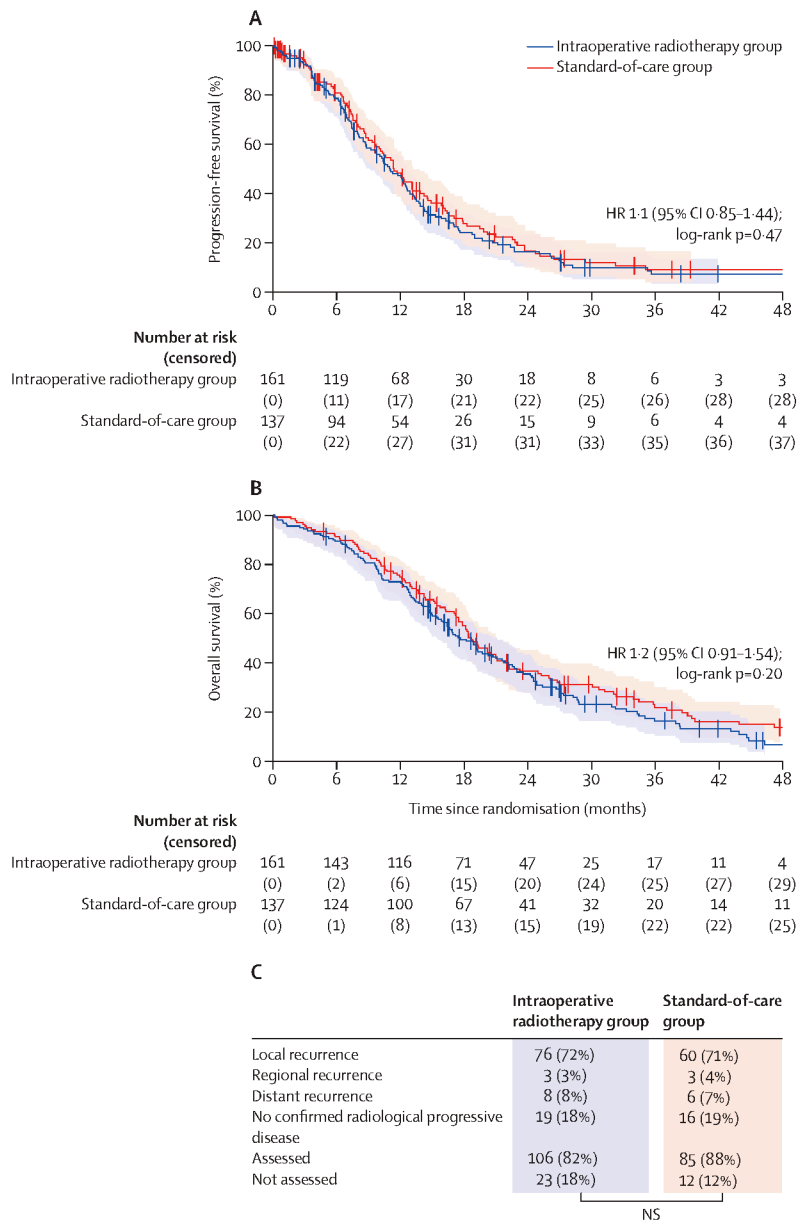


Figure 2: **Survival outcomes**
Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) among patients in the full-analysis set population. The 95% CIs are indicated by the shaded areas and vertical dashed lines represent censored patients. (C) Pattern of recurrence in both groups. Assessed refers to patients for whom centralised pattern-of-failure analysis was available at the time that the data safety monitoring board mandated the analysis of the primary endpoint, prioritising the central assessments for the patients who had reached the radiological progression-free survival endpoint. Not assessed refers to all other patients. Local, regional, and distant recurrence categories refer to the assessed population only. NS=not significant (p>0·05). HR=hazard ratio.

re-surgery with vital tumour (four [3%] intraoperative radiotherapy group *vs* four [4%] standard-of-care group). All reasons for censoring by treatment group are provided in the appendix (p 14). There were 129 deaths in the intraoperative radiotherapy group (116 not specified, 13 adverse event-related) and 104 deaths in the standard-of-care group (98 not specified, six adverse event-related; appendix pp 1–13). Median overall survival was 17·7 months (15·5–21·1) in the intraoperative radiotherapy group and 18·7 months (17·2–21·1) in the standard-of-care group (HR 1·2, 95% CI 0·91–1·54; p=0·20; figure 2B).

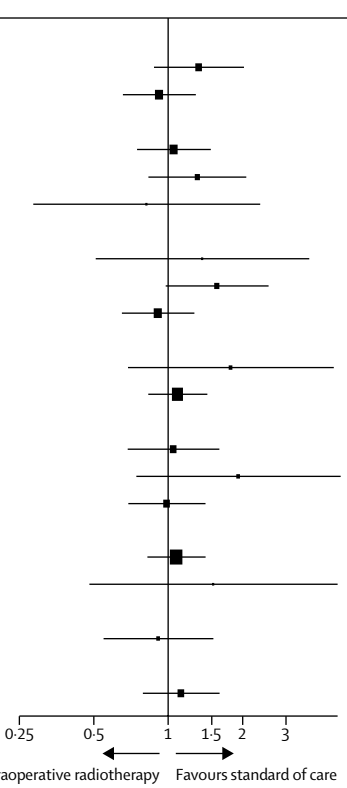
Central review for pattern-of-failure analysis was done on 106 (82%) evaluable cases in the intraoperative radiotherapy group and 85 (88%) in the standard-of-care group. Local recurrence, defined as within 1 cm of the resection cavity, was the predominant pattern of failure in both groups (76 [72%] of the assessed patients in the intraoperative radiotherapy group *vs* 60 [71%] in the standard-of-care group, p=0·87; figure 2C).

Subgroup analyses based on prespecified prognostic factors including sex, age, KPS, chemotherapy administration, MGMT methylation status, isocitrate dehydrogenase 1 mutation status, and residual disease revealed no significant difference between groups for progression-free survival (figure 3A) or overall survival (figure 3B).

The most common grade 1–2 adverse events were fatigue (69 [43%] patients in the intraoperative radiotherapy group *vs* 46 [34%] in the standard-of-care group), and headache (67 [42%] *vs* 47 [34%]; table 2). Grade 3–4 adverse events occurring in over 5% of patients included radiation necrosis (11 [7%] patients in the intraoperative radiotherapy group *vs* three [2%] in the standard-of-care group; table 2), seizures (21 [13%] *vs* nine [7%]), muscle weakness (12 [7%] *vs* 19 [14%]) and thrombocytopenia (seven [4%] *vs* 11 [8%]). The overall rate of other grade 3–4 adverse events analysed post hoc was 1·4 versus 1·2 events per patient, respectively. Wound complications were reported in eight (5%) patients in the intraoperative radiotherapy group versus two (1%) in the standard-of-care group, wound infections in six (4%) versus four (3%), and wound dehiscence in four (2%) versus none in the standard-of-care group. All wound-related events were grade 3 or below. In total, 252 serious adverse events occurred in 105 (65%) patients in the

A

	Intraoperative radiotherapy group		Standard-of-care group		Hazard ratio
	Events/n	Median progression-free survival, months (95% CI)	Events/n	Median progression-free survival, months (95% CI)	
Sex					
Female	50/64	12·4 (8·2–14·6)	39/63	13·1 (11·4–16·3)	1·33 (0·88–2·03)
Male	79/97	10·5 (8·5–12·6)	58/74	10·2 (7·8–12·1)	0·92 (0·66–1·29)
Age					
<65 years	76/97	11·8 (8·8–14·3)	57/76	13·1 (9·6–16·1)	1·06 (0·75–1·49)
65–75 years	47/55	10·5 (7·6–12·6)	31/47	11·4 (7·6–13·9)	1·31 (0·83–2·07)
>75 years	6/9	11·1 (0·4–NA)	9/14	9·0 (2·8–14·3)	0·82 (0·28–2·36)
Karnofsky performance score					
<70	10/12	12·2 (7·4–27·1)	7/11	11·1 (3·2–NA)	1·38 (0·51–3·73)
70–80	44/52	10·6 (7·6–12·3)	28/43	13·1 (10·0–16·5)	1·58 (0·98–2·55)
90–100	75/97	12·2 (8·5–13·9)	62/83	11·4 (8·0–13·9)	0·91 (0·65–1·28)
Chemotherapy					
No	11/16	2·5 (0·4–6·3)	8/17	3·2 (2·2–5·8)	1·79 (0·69–4·68)
Yes	118/145	12·1 (10·1–13·3)	89/120	12·1 (10·4–14·6)	1·09 (0·83–1·44)
***O*-6-methylguanine-DNA methyltransferase**					
Methylated	49/64	13·9 (12·1–17·5)	37/60	15·9 (11·4–22·6)	1·05 (0·69–1·61)
Unknown	10/12	9·7 (4·1–14·2)	8/14	21·0 (3·5–NA)	1·93 (0·74–4·99)
Unmethylated	70/85	8·7 (7·2–10·8)	52/63	9·6 (7·3–11·4)	0·99 (0·69–1·42)
Isocitrate dehydrogenase 1					
Mutation absent	121/150	10·6 (8·8–12·4)	92/128	11·4 (9·6–13·1)	1·08 (0·82–1·42)
Mutation present	8/11	17·1 (4·9–35·7)	5/7	22·8 (1·0–NA)	1·53 (0·48–4·85)
Residual tumour					
Measurable	35/35	7·2 (4·9–8·5)	27/27	7·6 (3·9–10·2)	0·91 (0·55–1·52)
Not measurable	3/3	8·7 (0·1–NA)	1/1	13·1 (NA–NA)	
Not present	69/69	10·8 (8·8–12·6)	55/57	11·4 (8·6–13·2)	1·13 (0·79–1·62)



(Figure 3 continues on next page)

B

	Intraoperative radiotherapy group		Standard-of-care group		Hazard ratio
	Events/n	Median overall survival, months (95% CI)	Events/n	Median overall survival, months (95% CI)	
Sex					
Female	46/64	19·3 (14·8–26·7)	44/63	19·3 (17·3–25·3)	1·04 (0·69–1·58)
Male	83/97	17·2 (14·6–21·2)	60/74	18·2 (14·4–21·8)	1·29 (0·92–1·81)
Age					
<65 years	71/97	22·6 (18·9–27·1)	52/76	22·3 (18·3–32·4)	1·16 (0·81–1·66)
65–75 years	49/55	13·3 (10·3–16·9)	39/47	17·9 (15·1–20·3)	1·53 (0·99–2·36)
>75 years	9/9	15·1 (0·4–22·2)	13/14	10·4 (5·1–17·5)	0·80 (0·33–1·96)
Karnofsky performance score					
<70	9/12	24·6 (10·0–NA)	6/11	36·0 (3·2–NA)	1·43 (0·49–4·21)
70–80	43/52	14·0 (9·8–16·9)	36/43	19·3 (16·3–23·3)	1·41(0·90–2·20)
90–100	77/97	19·3 (16·5–23·0)	62/83	18·7 (15·8–22·2)	1·09 (0·78–1·53)
Chemotherapy					
No	14/16	2·9 (0·9–9·7)	13/17	8·1 (3·2–18·4)	2·01 (0·92–4·39)
Yes	115/145	19·2 (16·7–22·6)	91/120	19·4 (17·9–22·3)	1·18 (0·89–1·55)
***O*-6-methylguanine-DNA methyltransferase**					
Methylated	47/64	24·3 (17·2–28·8)	40/60	26·1 (19·3–32·4)	1·20 (0·78–1·83)
Unknown	12/12	12·4 (5·3–28·9)	9/14	21·0 (10·6–NA)	2·44 (0·99–6·00)
Unmethylated	70/85	15·1 (12·8–19·2)	55/63	15·4 (12·9–18·4)	0·97 (0·68–1·38)
Isocitrate dehydrogenase 1					
Mutation absent	121/150	17·7 (15·0–21·2)	98/128	18·5 (17·1–21·0)	1·19 (0·91–1·56)
Mutation present	8/11	20·8 (6·6–54·8)	5/7	31·3 (6·3–NA)	1·27 (0·41–3·94)
Residual tumour					
Measurable	32/35	15·5 (10·3–22·8)	23/27	14·4 (10·2–20·3)	1·10 (0·64–1·89)
Not measurable	2/3	8·7 (0·1–NA)	1/1	25·0 (NA–NA)	1·14 (0·10–13·3)
Not present	65/69	17·0 (14·1–20·3)	52/57	18·9 (14·3–22·3)	1·33 (0·91–1·92)

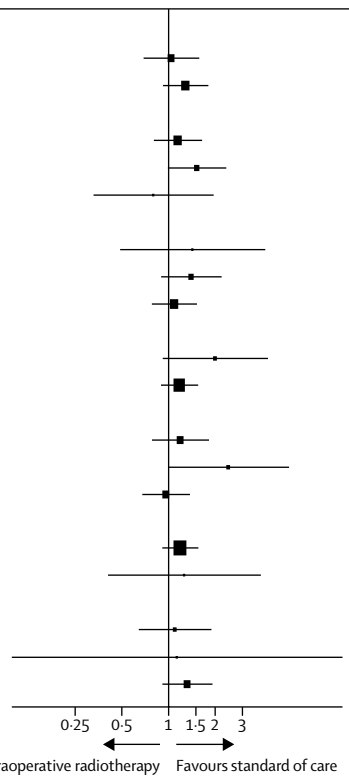


Figure 3: **Hazard ratios for progression-free and overall survival by clinical subgroup**
Forest plot of progression-free survival (A) and overall survival (B) in the full analysis set population. Square sizes are proportional to the number of patients in each subgroup. NA=no meaningful CI could be estimated.

intraoperative radiotherapy group and 142 serious adverse events in 72 (53%) patients in the standard-of-care group. Of these, 65 (26%) events in 40 (38%) patients in the intraoperative radiotherapy group and 27 (19%) events in 19 (26%) patients in the standard-of-care group were at least possibly related to the treatment. Of the grade 5 adverse events, 14 deaths in the intraoperative radiotherapy group (CNS toxicity [n=2], myocardial infarction [n=2], sepsis [n=2], and one each cardiac arrest, fever, lung infection, fracture, postoperative haemorrhage, neoplasm, haematoma, and not otherwise specified death) and six in the standard-of-care group (lung infection [n=2], and one each multiorgan failure, encephalitis, neoplasm, and cystitis) were attributable to specific CTCAE terms (table 2). Distribution of adverse event grades over time and the full adverse event listings are provided in the appendix (pp 1–13, 16).

Discussion

INTRAGO II was a large, international, open-label, randomised, controlled, phase 3 trial designed to evaluate whether a targeted, high single dose of radiation to the resection cavity delivered by use of low kilovolt intraoperative radiotherapy, in addition to the current standard of care, improves progression-free survival in patients with resectable, newly diagnosed glioblastoma. Overall, the study showed that dose intensification with a single, dose-escalated boost of 30 Gy did not result in improvement in progression-free survival or overall survival.

This randomised study contributes an important finding to the ongoing debate regarding the value of dose escalation for resectable, newly diagnosed glioblastoma, and more broadly challenges the underlying concept. Dose escalation in glioblastoma has a long history of phase 1/2 and small phase 2 randomised trials showing inconsistent and inconclusive results.[20] As early as 1979, Walker and colleagues demonstrated a dose–response relationship for external-beam radiotherapy up to 60 Gy, but no further survival benefit at higher doses.[21] Nelson and colleagues subsequently escalated doses to more than 80 Gy, confirming that

doses beyond 60 Gy increased toxicity without improving survival.[22] Brachytherapy boost strategies were evaluated in two randomised controlled trials that used ^{125}I implants,[10,23] both of which failed to show an overall survival benefit. Similarly, the RTOG 93-05 trial of a stereotactic radiosurgery boost before standard radiotherapy showed no improvement in survival or pattern of failure.[11] More recently, the NRG BN-001 phase 2, randomised trial of dose-escalated IMRT (75 Gy via simultaneous integrated boost) with concurrent temozolomide showed no survival benefit with photon-based dose intensification. Notably, the proton-based dose intensification group of this trial met the prespecified signal threshold for improved overall survival, although this was achieved at a relaxed type I error (α=0·15, p=0·11) and awaits confirmation in a planned phase 3 trial.[24]

Although the majority of earlier dose-escalation efforts did not result in a significant improvement in clinical outcomes, these negative findings have been interpreted with caution owing to heterogeneity in target delineation, dose conformity, and treatment delivery techniques. The

	Intraoperative radiotherapy group (n=161)				Standard-of-care group (n=137)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders								
Anaemia	14 (9%)	0	0	..	8 (6%)	2 (1%)	1 (1%)	..
Other, specify	5 (3%)	1 (1%)	..	..	6 (4%)	1 (1%)	..	..
Febrile neutropenia	..	1 (1%)	..	..	..	0	..	..
Cardiac disorders								
Atrial fibrillation	..	2 (1%)	..	..	..	0	..	..
Cardiac arrest	..	..	..	1 (1%)	..	..	..	0
Myocardial infarction	..	..	..	2 (1%)	..	..	..	0
Sinus tachycardia	3 (2%)	..	1 (1%)	..	1 (1%)	..	0	..
Eye disorders								
Cataract	1 (1%)	0	..	..	0	1 (1%)	..	..
Gastrointestinal disorders								
Abdominal pain	4 (2%)	0	..	..	..	1 (1%)	..	..
Other, specify	..	1 (1%)	..	..	..	0	..	..
Lower gastrointestinal haemorrhage	..	0	..	..	..	1 (1%)	..	..
Nausea	40 (25%)	1 (1%)	..	..	26 (19%)	2 (1%)	..	..
Vomiting	12 (7%)	2 (1%)	1 (1%)	..	3 (2%)	0	0	..
General disorders and administration site conditions								
Death	..	..	..	30 (19%)	..	..	..	19 (14%)
Fatigue	69 (43%)	4 (2%)	..	..	46 (34%)	4 (3%)	..	..
Fever	5 (3%)	1 (1%)	..	1 (1%)	2 (1%)	0	..	0
Gait disturbance	3 (2%)	0	..	..	2 (1%)	3 (2%)	..	..
Other, specify	2 (1%)	2 (1%)	..	..	2 (1%)	2 (1%)	..	..
Malaise	1 (1%)	2 (1%)	..	..	2 (1%)	0	..	..
Multiorgan failure	..	..	..	0	..	..	..	1 (1%)
Oedema trunk	..	3 (2%)	..	..	..	0	..	..
Pain	..	1 (1%)	..	..	7 (5%)	0	..	..
Hepatobiliary disorders								
Cholecystitis	..	..	0	..	..	..	1 (1%)	..
Infections and infestations								
Encephalitis infection	..	1 (1%)	..	0	..	1 (1%)	..	1 (1%)
Endocarditis infective	..	1 (1%)	..	..	..	0	..	..
Enterocolitis infectious	4 (2%)	0	..	..	..	1 (1%)	..	..
Lung infection	..	5 (3%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0	2 (1%)
Meningitis	..	1 (1%)	1 (1%)	..	..	0	1 (1%)	..
Sepsis	..	1 (1%)	1 (1%)	2 (1%)	..	0	0	0
Skin infection	3 (2%)	0	..	..	2 (1%)	1 (1%)	..	..
Urinary tract infection	5 (3%)	5 (3%)	1 (1%)	..	3 (2%)	2 (1%)	0	..
Wound infection	1 (1%)	5 (3%)	..	..	1 (1%)	3 (2%)	..	..

(Table 2 continues on next page)

NRG BN-001 trial has reignited debate regarding the potential role of dose escalation that uses a high-linear energy transfer modality. Similar to proton therapy, low-energy X-ray intraoperative radiotherapy achieves a steep dose gradient, enabling precise local dose delivery with efficient sparing of deeper healthy tissue with high or higher linear energy transfer.[25] In addition, unlike adjuvant external-beam radiotherapy techniques, intraoperative radiotherapy provides the additional advantage of immediate tumour cell eradication at the resection cavity similar to brachytherapy and preoperative stereotactic radiosurgery approaches, allowing earlier initiation of postoperative radiotherapy in order to prevent rapid tumour regrowth. A single, high-dose radiation boost might induce complex DNA damage leading to immune responses and might have potential in combined immunomodulatory approaches.

Intriguingly, local dose escalation also did not alter the pattern of failure in this trial, as approximately 70% of recurrences occurred within 1 cm of the resection cavity in both groups, which is largely consistent with historical data.[6] The irradiation system used in this trial produces a

	Intraoperative radiotherapy group (n=161)				Standard-of-care group (n=137)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Injury, poisoning, and procedural complications								
Ankle fracture	..	1 (1%)	..	..	..	0	..	..
Arterial injury	..	1 (1%)	..	..	..	0	..	..
Dermatitis radiation	15 (9%)	..	..	..	18 (13%)	..	..	..
Fall	..	2 (1%)	..	..	..	2 (1%)	..	..
Fracture	..	0	..	1 (1%)	..	1 (1%)	..	0
Other, specify	..	0	..	..	..	1 (1%)	..	..
Intraoperative haemorrhage	1 (1%)	..	1 (1%)	..	..	..	0	..
Intraoperative neurological injury	6 (4%)	1 (1%)	..	..	..	3 (2%)	..	..
Intraoperative venous injury	..	0	..	..	..	1 (1%)	..	..
Postoperative haemorrhage	4 (2%)	3 (2%)	0	1 (1%)	..	1 (1%)	3 (2%)	0
Vascular access complication	..	1 (1%)	..	..	..	0	..	..
Wound complication	5 (3%)	3 (2%)	..	..	..	1 (1%)	..	..
Wound dehiscence	2 (1%)	2 (1%)	..	..	..	0	..	..
Investigations								
Alanine aminotransferase increased	10 (6%)	3 (2%)	..	..	3 (2%)	0	..	..
Creatinine increased	6 (4%)	1 (1%)	..	..	2 (1%)	0	..	..
Gamma-glutamyl transferase increased	2 (1%)	1 (1%)	..	..	2 (1%)	2 (1%)	..	..
Other, specify	9 (6%)	2 (1%)	..	1 (1%)	9 (7%)	0	..	0
Lymphocyte count decreased	3 (2%)	0	0	..	3 (2%)	1 (1%)	2 (1%)	..
Neutrophil count decreased	0	0	1 (1%)	..	1 (1%)	1 (1%)	2 (1%)	..
Thrombocytopenia	16 (10%)	5 (3%)	2 (1%)	..	23 (17%)	7 (5%)	4 (3%)	
Weight loss	8 (5%)	1 (1%)	..	..	2 (1%)	1 (1%)	..	..
White blood cell decreased	3 (2%)	4 (2%)	1 (1%)	..	9 (7%)	3 (2%)	2 (1%)	..
Metabolism and nutrition disorders								
Dehydration	2 (1%)	3 (2%)	..	..	0	1 (1%)	..	..
Hyperglycaemia	7 (4%)	2 (1%)	2 (1%)	..	2 (1%)	2 (1%)	0	..
Hypokalaemia	4 (2%)	1 (1%)	..	..	5 (4%)	2 (1%)	..	..
Hyponatraemia	7 (4%)	0	..	..	3 (2%)	1 (1%)	..	..
Musculoskeletal and connective tissue disorders								
Arthritis	1 (1%)	0	..	..	0	1 (1%)	..	..
Generalised muscle weakness	3 (2%)	2 (1%)	..	..	7 (5%)	3 (2%)	..	..
Muscle weakness left-sided	12 (7%)	4 (2%)	0	..	3 (2%)	7 (5%)	3 (2%)	..
Muscle weakness lower limb	9 (6%)	3 (2%)	1 (1%)	..	3 (2%)	1 (1%)	0	..
Muscle weakness right-sided	2 (1%)	1 (1%)	0	..	4 (3%)	4 (3%)	1 (1%)	..
Muscle weakness upper limb	3 (2%)	1 (1%)	..	..	0	0	..	..
Neoplasms benign, malignant, and unspecified (including cysts and polyps)								
All neoplasms	1 (1%)	2 (1%)	..	1 (1%)	1 (1%)	5 (4%)	..	1 (1%)

(Table 2 continues on next page)

	Intraoperative radiotherapy group (n=161)				Standard-of-care group (n=137)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Nervous system disorders								
Gait disturbance	..	1 (1%)	..	..	..	1 (1%)	..	..
Amnesia	2 (1%)	0	..	..	4 (3%)	2 (1%)	..	..
Aphonia	3 (2%)	1 (1%)	..	..	0	0	..	..
Ataxia	6 (4%)	4 (2%)	..	..	4 (3%)	2 (1%)	..	..
Cerebrospinal fluid leakage	0	0	..	..	3 (2%)	1 (1%)	..	..
Cognitive disturbance	8 (5%)	4 (2%)	1 (1%)	..	9 (7%)	3 (2%)	1 (1%)	..
Depressed level of consciousness	1 (1%)	3 (2%)	..	..	0	0	..	..
Dizziness	17 (11%)	0	1 (1%)	..	11 (8%)	1 (1%)	0	..
Dysarthria	9 (6%)	2 (1%)	..	..	7 (5%)	1 (1%)	..	..
Dysaesthesia	3 (2%)	1 (1%)	..	..	4 (3%)	0	..	..
Dysphasia	15 (9%)	7 (4%)	..	..	13 (9%)	6 (4%)	..	..
Encephalopathy	..	1 (1%)	..	..	..	0	..	..
Facial muscle weakness	3 (2%)	0	..	..	0	1 (1%)	..	..
Facial nerve disorder	4 (2%)	2 (1%)	..	..	4 (3%)	0	..	..
Headache	67 (42%)	3 (2%)	..	..	47 (34%)	6 (4%)	..	..
Hydrocephalus	1 (1%)	2 (1%)	2 (1%)	..	1 (1%)	0	1 (1%)	..
Intracranial haemorrhage	..	2 (1%)	3 (2%)	..	2 (1%)	0	1 (1%)	..
Lethargy	..	1 (1%)	..	..	2 (1%)	0	..	..
Memory impairment	17 (11%)	1 (1%)	1 (1%)	..	13 (9%)	1 (1%)	1 (1%)	..
Other, specify	19 (12%)	6 (4%)	2 (1%)	2 (1%)	14 (10%)	4 (3%)	0	0
Oculomotor nerve disorder	1 (1%)	1 (1%)	..	..	1 (1%)	0	..	..
Oedema cerebral	8 (5%)	6 (4%)	1 (1%)	..	6 (4%)	2 (1%)	2 (1%)	..
Paraesthesia	12 (7%)	1 (1%)	..	..	..	0	..	..
Pyramidal tract syndrome	6 (4%)	5 (3%)	1 (1%)	..	3 (2%)	2 (1%)	0	..
Radiation necrosis	9 (6%)	10 (6%)	1 (1%)	..	6 (4%)	3 (2%)	0	..
Seizure	32 (20%)	20 (12%)	1 (1%)	..	22 (16%)	8 (6%)	1 (1%)	..
Somnolence	3 (2%)	1 (1%)	1 (1%)	..	1 (1%)	3 (2%)	0	..
Stroke	1 (1%)	..	1 (1%)	..	0	..	0	..
Syncope	1 (1%)	4 (2%)	..	..	1 (1%)	2 (1%)	..	..
Tremor	4 (2%)	0	..	..	4 (3%)	1 (1%)	..	..
Vasovagal reaction	..	1 (1%)	..	..	..	0	..	..
Psychiatric disorders								
Confusion	7 (4%)	3 (2%)	..	..	7 (5%)	1 (1%)	..	..
Delirium	..	0	..	..	..	1 (1%)	..	..
Depression	8 (5%)	..	1 (1%)	..	1 (1%)	..	0	..
Psychosis	0	0	..	..	..	1 (1%)	..	..
Suicide attempt	..	..	1 (1%)	..	..	..	0	..
Renal and urinary disorders								
Acute kidney injury	1 (1%)	1 (1%)	..	..	0	0	..	..
Other, specify	0	..	..	0	1 (1%)	..	..	1 (1%)
Urinary incontinence	6 (4%)	0	..	..	2 (1%)	1 (1%)	..	..
Urinary tract pain	2 (1%)	1 (1%)	..	..	0	0	..	..
Respiratory, thoracic, and mediastinal disorders								
Aspiration	2 (1%)	1 (1%)	..	..	0	0	..	..
Hiccups	..	1 (1%)	..	..	..	0	..	..
Pneumonitis	2 (1%)	..	1 (1%)	..	0	..	1 (1%)	..

(Table 2 continues on next page)

	Intraoperative radiotherapy group (n=161)				Standard-of-care group (n=137)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Skin and subcutaneous tissue disorders								
Alopecia	36 (22%)	4 (2%)	..	..	37 (27%)	0	..	..
Dry skin	4 (2%)	0	..	..	4 (3%)	1 (1%)	..	..
Erythroderma	5 (3%)	0	..	..	6 (4%)	1 (1%)	..	..
Skin ulceration	2 (1%)	1 (1%)	..	..	0	0	..	..
Surgical and medical procedures								
Other, specify	1 (1%)	1 (1%)	..	..	2 (1%)	2 (1%)	..	..
Vascular disorders								
Haematoma	1 (1%)	1 (1%)	1 (1%)	1 (1%)	2 (1%)	0	0	0
Thromboembolic event	9 (6%)	4 (2%)	3 (2%)	3 (2%)	3 (2%)	3 (2%)	2 (1%)	..
Other, specify	1 (1%)	1 (1%)	..	..	0	0	..	..

Data are n (%). Adverse events reported per treatment arm according to the Common Terminology Criteria for Adverse Events, version 4.0. Grade 1–2 adverse events occurring in at least 10% of patients are shown. All grade 3, 4, and 5 adverse events are reported. Repeated occurrence of the same adverse event in an individual patient was allowed.

Table 2: **Acute and late adverse events**

steep dose gradient characteristic of 50 kV photons: the prescribed 30 Gy surface dose attenuates rapidly, reaching approximately 12 Gy at 5 mm and 5–7 Gy at 10 mm depth from the applicator surface, depending on applicator diameter. This dose distribution effectively confines therapeutic dose delivery to a narrow rim of tissue immediately adjacent to the resection cavity, potentially leaving infiltrating tumour cells at greater depths.

Given that glioblastoma cells are known to infiltrate several centimetres beyond the contrast-enhancing margin,[26] this fundamental geometric mismatch between the rather surface-confined intraoperative radiotherapy treatment volume[27] and the true extent of microscopic disease represents an inherent and insurmountable limitation of any cavity-directed boost approach. However, even within the high-dose zone where tumour cells were unequivocally within the therapeutic isodose surface (ie, in patients with measurable residual disease), no meaningful treatment effect signal was detectable. This unexpected finding gives rise to several hypotheses. First, residual glioblastoma cells might exhibit far greater intrinsic radioresistance than previously appreciated,[28] limiting the potential benefit of focal dose intensification. Second, intraoperative radiotherapy might induce biological alterations within the pericavitary microenvironment, such as changes in vascular permeability, inflammatory signalling, or hypoxic stress responses, which might inadvertently support residual tumour survival, proliferation or migration.[7,29,30] Third, the additional radiation dose might further eradicate immune cells and cytokines that are critical for early postsurgical antitumour activity, including recently described cranioencephalic lymphoid units involved in glioblastoma immune surveillance.[31] In addition, by inducing endothelial injury and radiation-associated vasculopathy, intraoperative radiotherapy might reduce functional microvasculature around the cavity, thereby impairing effective trafficking and penetration of effector immune cells into the irradiated pericavitary rim. These mechanisms are not mutually exclusive and might interact to diminish the anticipated therapeutic advantage of intraoperative radiotherapy, highlighting the need to elucidate their relative contributions in order to optimise patient selection and future strategies for local dose intensification.

Alternative approaches to local dose intensification are under investigation, including surgically implanted ^{131}CS brachytherapy tiles,[32] balloon-based intracavitary brachytherapy,[33] and targeted radionuclide therapy.[34] Although these modalities deliver protracted low-dose-rate irradiation over days to weeks, they share the fundamental limitation of being cavity-directed and therefore subject to the same geometric mismatch with the infiltrative extent of glioblastoma. To date, none of these approaches has shown level I evidence of efficacy in randomised trials.

One could argue that progression-free survival as a primary endpoint in glioblastoma trials remains inherently limited by the difficulty of reliably distinguishing true progression from treatment-related changes. To mitigate this, INTRAGO-II used masked, centralised, neuroradiological review incorporating quantitative dynamic susceptibility contrast perfusion analysis. Importantly, the concordance between the negative progression-free survival result and the equally negative overall survival outcome provides strong internal validation of the primary finding and argues against a scenario in which pseudoprogression in the intraoperative radiotherapy group selectively confounded the progression-free survival analysis.

Previous reports on intraoperative radiotherapy for brain metastases suggest a favourable toxicity profile, with particularly low rates of radionecrosis compared with EBRT,[35] even in settings with concomitant immunotherapy.[36] Consistent with these reports, only a modest increase in toxicity was observed in INTRAGO-II, with an overall grade 3 or worse radiation necrosis rate of 7%, despite the dose-escalation approach. Notably, only one grade 4 radiation necrosis event occurred. Although a higher incidence of adverse events was observed in the intraoperative radiotherapy group, this might be attributable to the higher frequency of study visits in this group caused by the higher discontinuation rate in the control group. This is also reflected in the observed rates of grade 3 or worse seizures (13% intraoperative radiotherapy group *vs* 7% standard-of-care group, p=0·064), which, however, were not significantly different between groups and still within the range reported in other glioblastoma trials.[4] Equally, a trend towards a higher rate of hyperglycaemia was observed in the intraoperative radiotherapy group, which might have been caused by higher corticosteroid doses. To further elucidate this, we did a detailed review of all hyperglycaemia events, which revealed that the numerical imbalance between groups was attributable to a heterogeneous combination of perioperative glucose fluctuations, pre-existing diabetes, and corticosteroid use, the latter of which was observed in both treatment groups. Although systematic corticosteroid documentation outside of RANO was not a protocol-specified variable, the available data do not support a causal relationship between intraoperative radiotherapy and increased steroid-induced hyperglycaemia. In summary, INTRAGO-II did not result in unexpected toxicity and thus confirms earlier data. Following reports in patients with brain metastases,[37] intraoperative radiotherapy as an adjunct to standard of care might enable a reduction in external-beam radiotherapy fractions, thus shortening overall treatment duration and potentially reducing treatment burden. This hypothesis, however, warrants evaluation in a prospective trial.

There are several limitations to the trial. First, intraoperative radiotherapy is a highly conformal technique but is subject to considerable variability in applicator placement, limited by cavity size and geometry, which requires a substantial learning curve for optimal dose delivery. To mitigate this, INTRAGO-II implemented several quality control and monitoring measures across experienced centres to ensure consistency in treatment application. Second, 47 (16%) participants discontinued the trial before reaching the study endpoint, which is, however, in the expected range in oncology trials[38] and remained similar to landmark trials in glioblastoma such as the EORTC 26981 study (approximately 85% completion of chemoradiotherapy).[39] Yet, the inherently open-label design of INTRAGO-II probably exacerbated differential attrition: control group patients who were aware of not receiving intraoperative radiotherapy might have been more inclined to discontinue study follow-up in favour of exploring alternative treatment options, including enrolment in competing clinical trials. This is reflected in the asymmetric discontinuation rates (20% standard of care group *vs* 12% intraoperative radiotherapy group). The numerically higher completion rate in the intraoperative radiotherapy group compared with the control group might reflect a motivational effect of having received the experimental intervention, potentially increasing patient commitment to completing the full treatment course, which is a recognised phenomenon in open-label oncology trials. We also cannot exclude an influence of other factors. For instance, INTRAGO-II included patients with KPS as low as 60%, a population at higher risk of clinical deterioration during adjuvant treatment, who were not included in many registration trials. Furthermore, a substantial portion of enrolment and follow-up coincided with the COVID-19 pandemic, which disrupted treatment delivery at multiple sites.

Notably, the INTRAGO-II results also mirror a recurring pattern in glioblastoma research: promising outcomes from small, uncontrolled studies compared with historical controls that do not withstand the scrutiny of adequately powered randomised evaluation. The preceding INTRAGO-I phase 1/2 trial (n=15) and international pooled analysis (n=51) both suggested favourable progression-free survival and overall survival relative to historical benchmarks.[16,17] The INTRAGO-II trial underscores that historical comparisons, however carefully curated, remain an unreliable basis for estimating treatment effects in glioblastoma and cannot substitute for randomised evidence.

In conclusion, INTRAGO-II provides level I evidence that the addition of an immediate, targeted, high single dose of radiotherapy to standard-of-care management in patients with resectable, newly diagnosed glioblastoma does not improve oncological outcomes or local tumour control, further challenging the broader concept of dose escalation in glioblastoma. The trial results emphasise the pressing need to refine our understanding of the biological determinants of glioblastoma radioresistance and improved patient selection for radiation dose-escalation treatment approaches.

Contributors

This study was conceptualised and conceived by FAG, KP, WBP, and FW. All authors treated patients. WBP assessed and reviewed the patient's imaging. Material preparation and data analysis were done by JPL and AMR. The first draft of the manuscript was written by JPL and GRS. Tables and figures were created by JPL and AMR. FAG, CIT, and KP reviewed and edited the data and manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. FAG, JPL, and KP accessed and verified the data.

Declaration of interests

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Data sharing

Access to clinical trial data, such as anonymised, individual, and trial-level data (analysis data sets), as well as other information (such as protocols, clinical study reports, analysis plans, and data dictionaries), can be requested via email to the corresponding author by any qualified researcher who engages in rigorous, independent, scientific research. These data will be provided following review and approval of a research proposal, statistical analysis plan, and execution of a data sharing agreement. The study protocol is made available in the appendix.

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