O-(2-[^{18}F]fluoroethyl)-L-tyrosine-PET-guided versus contrast-enhanced T1-weighted MRI-guided re-irradiation in patients with recurrent glioblastoma (GLIAA/NOA-10 ARO2013-01): a multicentre, open-label, randomised trial

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Summary

Background O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET)-PET has a higher specificity than contrast-enhanced T1-weighted MRI (CE-T1MRI) in diagnosing recurrent glioblastoma. We aimed to evaluate whether a FET-PET-based target volume delineation, compared with CE-T1MRI, improves outcomes in patients with recurrent glioblastoma scheduled for re-irradiation.

Methods GLIAA was a multicentre, open-label, parallel randomised study done in 15 radiation oncology centres in Germany. Patients aged 18 years or older with a Karnofsky performance score greater than 60% and a macroscopic WHO grade IV recurrent glioblastoma (1–6 cm) were randomly assigned (1:1) to receive either FET-PET-based or CE-T1MRI-based target volume delineation followed by re-irradiation with 39 Gy in 13 fractions. Randomisation was performed centrally, using a minimisation technique with a random element and a computer-assisted randomisation tool, stratified by time since first radiotherapy, previous chemotherapy, tumour diameter, MGMT status, and planned chemotherapy. The primary endpoint was progression-free survival from randomisation, assessed in the per-protocol population (patients who initiated treatment per their assigned group). Adverse events were systematically assessed in all patients who commenced therapy. The trial was registered with ClinicalTrials.gov (NCT01252459), German Clinical Trials Registry (DRKS00000634), and European Clinical Trials Database (EudraCT 2012–001121–27), and is completed.

Findings Between Nov 22, 2013, and Aug 18, 2021, 271 patients were recruited and screened for eligibility, 200 of whom were randomly assigned to re-irradiation based on FET-PET (n=100) or CE-T1MRI (n=100). 85 (43%) participants were female and 115 (58%) were male. 98 patients in the FET-PET group and 97 in the CE-T1MRI group were treated per protocol. Median follow-up for censored patients was 12·2 months (IQR 6·6-20·7). Median progression-free survival was 4·0 months (95% CI 3·7–5·2) in the FET-PET group and 4·9 months (3·7–6·0) in the CE-T1MRI group (one-sided stratified log-rank p=0·98; adjusted hazard ratio 1·14 [95% CI 0·85–1·52]; p=0·39; median follow-up for six censored patients 4·1 months [IQR 2·3–6·6]). The most common grade 3–4 adverse event was radionecrosis (eight [8%] of 99 in the FET-PET group *vs* seven [7%] of 99 in the CE-T1MRI group). Acute and subacute serious adverse events occurred in 15 (15%) of 99 patients in each group; possibly re-irradiation-related late serious adverse events occurred in ten (10%) of 97 patients in the FET-PET group and 18 (19%) of 96 in the CE-T1MRI group. There were no treatment-related deaths.

Interpretation FET-PET-based target volume delineation for re-irradiation did not lead to a significant clinical benefit compared with CE-T1MRI-based treatment in patients with recurrent glioblastoma. Thus, CE-T1MRI remains the preferred delineation method in this setting.

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Introduction

Advances in radiation oncology have been marked by the development of sophisticated techniques that enable high precision in treatment application. However, such high precision only yields real clinical benefits if the target volume is correctly defined. Innovations in imaging have the potential to improve tumour delineation and thus enhance the efficacy of radiotherapy.

Achieving therapeutic success in glioblastoma remains one of the most difficult endeavours in neuro-oncology.

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Research in context

Evidence before this study

We searched PubMed from database inception to April 30, 2025, using combinations of the terms "glioblastoma", "recurrent", "radiation", "re-irradiation", "PET", and "clinical trials", for publications in any language. Re-irradiation was shown in three systematic reviews to be an established treatment option for recurrent high-grade gliomas. Four prospective, single-institution trials investigated the use of amino-acid PET for radiotherapy planning in this context, showing that the method is safe and feasible. Moreover, multiple histology-based studies showed higher sensitivity and specificity of amino-acid PET compared with contrast-enhanced MRI in identifying the presence and extent of gliomas and recurrent gliomas. Studies by our group have shown substantial differences between gross tumour volumes of gliomas and recurrent high-grade gliomas defined on contrast-enhanced MRI and amino-acid PET. A retrospective analysis also suggested that re-irradiation based on amino-acid PET might improve treatment outcomes. However, to our knowledge, no clinical trial has prospectively compared amino-acid PET-based versus MRI-based re-irradiation.

Added value of this study

Imaging studies are essential for high precision radiotherapy. Treatment of recurrent glioblastoma represents a major challenge in neuro-oncology. Re-irradiation is a therapeutic option for localised recurrences, but precise target volume definition is challenging due to the high radiosensitivity of normal brain tissue, the radioresistance of glioblastoma, and the limitations of MRI in distinguishing recurrent tumour from post-treatment changes. To our knowledge, this is the first prospective, randomised trial to evaluate the value of biological imaging with amino-acid PET for radiotherapy planning in this setting. The study investigated a target volume delineation approach based solely on O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET)-PET and compared oncological outcomes with the conventional contrast-enhanced MRI-based method used in clinical practice.

Implications of all the available evidence

This study documents favourable tumour control after re-irradiation in patients with recurrent glioblastoma and shows the feasibility and safety of incorporating biological imaging into radiotherapy planning. However, defining target volumes using FET-PET did not lead to improved patient outcomes after re-irradiation, despite the well documented high sensitivity and specificity of FET-PET compared with contrast-enhanced T1-weighted MRI for detecting recurrent glioblastoma. As described in previous studies, target volumes delineated with FET-PET are different from those defined by contrast-enhanced MRI. However, this difference does not appear to be large enough to affect clinical outcomes after re-irradiation.

Following initial multimodal treatment, the interpretation of follow-up imaging is often challenging, as both recurrent glioblastoma and treatment-related changes can show similar features on MRI. This ambiguity complicates decisions regarding re-irradiation and the appropriate definition of the target volume. Especially in the case of in-field re-irradiation, small volumes and precise targeting are of utmost importance to avoid toxicity.

Contrast-enhanced T1-weighted MRI (CE-T1MRI) plays a key role in the diagnosis of high-grade gliomas[1,2] and thus in defining target volumes for radiotherapy. However, multiple studies have shown a higher sensitivity and specificity of the amino-acid PET examination compared with CE-T1MRI, especially in pretreated tumours.[3–5] Although earlier studies have investigated the amino-acid PET tracer [^{11}C]methionine,[5] O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET), with its longer half-life, is now more frequently used in routine clinical practice in Europe and provides equivalent information in clinical settings.[3–8]

Studies have shown that tumour volumes defined on amino-acid PET and CE-T1MRI can differ substantially.[9,10] A case series from our group investigated the role of amino-acid PET and single photon-emission CT in re-irradiation and showed a potential survival advantage in patients with recurrent high-grade glioma whose radiotherapy planning incorporated amino-acid imaging compared with those treated using MRI alone.[11] These data generated the hypothesis that amino-acid PET-based re-irradiation might help improve oncological outcomes in patients with recurrent glioblastoma. A pilot trial[12] was initiated to assess the differences in radiation target volume as defined by either CE-T1MRI or FET-PET. This trial showed a significant difference in size and location between the two volumes, with FET-uptake best predicting the location of further tumour progression.[12]

Therefore, we aimed to assess the effect on patient outcome of a FET-PET-based compared with a CE-T1MRI-based target volume delineation for the re-irradiation of recurrent glioblastoma in a larger, randomised trial.

Methods

Study design and participants

GLIAA was a multicentre, open-label, parallel randomised study[13] done in 15 radiation oncology centres in Germany (appendix p 1). The trial was approved by the Ethics Committee of the University of Freiburg on April 24, 2013 (EK-Freiburg 133/10), and two subsequent amendments were approved. The trial was reviewed and approved by the German Federal Office for Radiation Protection and the German Federal Institute for Drugs and Medical Devices. Patient representatives were informed on study design, conduct, and interpretation of

results within the Neuro-Oncological Working Group of the German Cancer Society. The trial was registered with ClinicalTrials.gov (NCT01252459), German Clinical Trials Registry (DRKS00000634), and European Clinical Trials Database (EudraCT 2012–001121–27). The status of the study is completed.

Patients aged 18 years or older with a Karnofsky performance score greater than 60% and a macroscopic WHO grade IV recurrent glioblastoma (2007 and 2016 WHO classifications[14,15]) histologically confirmed at first diagnosis or recurrence, with lesion size of 1–6 cm on CE-T1MRI and FET-PET, who had received radiotherapy with 59·4–60 Gy (1·8–2 Gy fractions) to the same site at least 6 months earlier, were included. Patients with negative histology within the past 4 weeks, previous targeted therapy within 6 months, or inability to undergo FET-PET or MRI were excluded. Inclusion was irrespective of recurrence therapy line. For patients who had undergone resection, re-irradiation started 3 or more weeks after surgery. Planned parallel and sequential chemotherapy with temozolomide, lomustine, or both, was allowed as of the protocol amendment of May 24, 2018. All patients provided written informed consent. Potential bias was minimised by randomisation and adherence to predefined inclusion and exclusion criteria (appendix p 1). Sex data were documented from electronic medical records; race and ethnicity data were not collected.

Randomisation and masking

Randomisation was done after screening and both CE-T1MRI and FET-PET imaging within a time span of 2 weeks. Patients were randomly assigned (1:1) to receive FET-PET-based re-irradiation (experimental group) or CE-T1MRI-based re-irradiation (control group). Randomisation was performed centrally, using a minimisation technique with a random element and a computer-assisted randomisation tool (Randomizer), stratified by time since first radiotherapy, previous chemotherapy, tumour diameter, MGMT status, and planned chemotherapy (appendix p 2). An open-label design was chosen because effective masking would not have been feasible.

Procedures

The FET tracer was centrally produced by an authorised manufacturer, EuroPET (Freiburg, Germany), and delivered to all participating centres. PET–CT phantom studies were performed at each site to harmonise acquisition and reconstruction parameters in terms of image quality and resolution with the reference centre in Freiburg. For PET imaging, patients were injected with 200–300 MBq carrier-free FET and a static scan of 10–20 min duration was acquired 15 min post-injection.

A study-specific MRI protocol was provided to all investigators, requiring a minimum 1·5 Tesla MR-scanner, acquisition of axial T2 or fluid-attenuated inversion recovery (FLAIR) and axial or three-dimensional (3D) T1-weighed sequences before and after gadolinium-based contrast administration (5 min minimum time between injection and imaging). Minimal slice thickness was 3 mm for two dimensional sequences and 1 mm for 3D isotropic sequences. Optional advanced MRI sequences were permitted, but only the 3D-CE-T1MRI-sequence was allowed to be used for radiotherapy planning.

FET-PET and CE-T1MRI were rigidly co-registered with the planning CT as described previously.[11] A gross tumour volume based on FET-PET and one based on 3D-CE-T1MRI were defined for all patients. Briefly, for FET-PET, it was recommended that voxels with at least 1·8-times higher standardised uptake value than in contralateral brain tissue be included in the gross tumour volume as a starting point. The volume was then visually reviewed and adjusted by the treating radiation oncologist and nuclear medicine specialist. Details of the target volume definition are described in the study protocol (appendix p 57).[13] For the gross tumour volume based on CE-T1MRI, all tumour-related contrast-enhancing lesions were included based on the assessment of the treating radiation oncologist. Each volume was delineated irrespective of the volume depicted by the other imaging modality.

All subsequent steps were identical for both treatment groups, but initiated only from the gross tumour volume according to the assigned group. The clinical target volume was defined by adding 3 mm in all directions, respecting anatomical boundaries such as the skull, falx, ventricles, or tentorium. The clinical target volume was then expanded to the planning target volume by adding 1–2 mm in all directions, considering the treatment precision of each institution. MRI–CT-based contouring of predefined organs at risk was performed.

After randomisation, re-irradiation was planned based on the defined planning target volume for the assigned treatment group. Stereotactic re-irradiation was planned with a total dose of 39 Gy in 13 fractions of 3 Gy per day, five times per week (equivalent dose in 2 Gy fractions $[EQD2]_{\alpha/\beta=2\ Gy}$=48·75 Gy, $EQD2_{\alpha/\beta=10\ Gy}$=42·25 Gy). The dose, chosen due to the favourable EQD2 values and based on the cumulative brain radiation tolerance,[16] was prescribed according to the criteria of the International Commission on Radiation Units and Measurements, with 95% of the dose encompassing the planning target volume. Radiotherapy planning and organs at risk constraints were defined per protocol. Organs at risk constraints (appendix p 3) refer to cumulative doses from current and previous radiotherapy at the same site, calculated as $EQD2_{\alpha/\beta=2\ Gy}$. Image-guided radiotherapy was used, with thermoplastic head fixation. All radiotherapy plans underwent quality assurance according to protocol-defined criteria for stereotactic fractionated radiotherapy at the reference site in Freiburg.

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See **Online** for appendix

For **Randomizer** see https://www.randomizer.at/

Response was evaluated locally using MRI at 6 and 12 weeks after re-irradiation and every 3 months thereafter. Progression on imaging was diagnosed according to Response Assessment in Neuro-Oncology (RANO) criteria. Suspicion of progression was confirmed using FET-PET or histology whenever possible. Administration of any new antitumour therapy, including bevacizumab, but excluding surgery for radionecrosis, was considered an event for progression-free survival, even in the absence of confirmed progression.

To assess the safety of FET application, adverse events were recorded up to 7 days after FET-PET imaging. Prespecified adverse events considered as possible radiotherapy-related were documented according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03) during treatment and follow-up. Adverse events occurring within 90 days of radiotherapy initiation were considered acute or subacute, those beyond 90 days until the end of follow-up were considered late adverse events. All serious adverse events within 30 days after radiotherapy completion and all radiotherapy-related serious adverse events during the entire follow-up were recorded. Investigators were instructed to distinguish as accurately as possible between treatment-related toxicity and tumour-related symptoms. In all cases of suspected progression or radionecrosis on MRI, decisions were made on a case-by-case basis, with investigators being advised to perform FET-PET or, when feasible, attempt histological confirmation. Investigators were directed to administer corticosteroids and conduct serial multiparametric MRI scans to support an accurate differential diagnosis.

Criteria for early removal from trial are shown in the appendix (p 3). Thereafter, patients were followed-up according to standard of care.

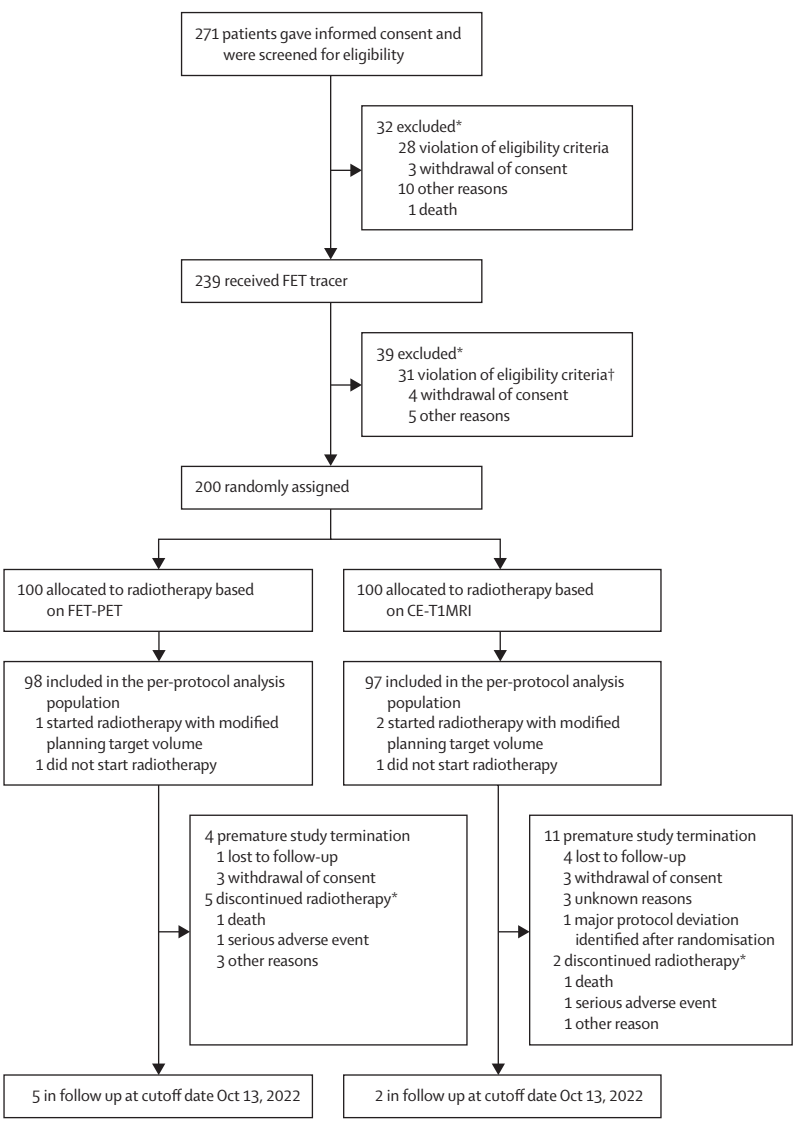

Figure 1: **Trial profile**
CE-T1MRI=contrast-enhanced T1-weighted MRI. FET=O-(2-[^{18}F]fluoroethyl)-L-tyrosine. *Some patients had more than one reason for exclusion or treatment discontinuation. †n=7 absent FET uptake, n=18 FET uptake >6 cm.

Outcomes

The primary endpoint was progression-free survival from the date of randomisation until disease progression or death.

Secondary endpoints were safety; overall survival, defined as the time from randomisation to death; volumetric analysis of co-registered MRI and PET target volumes; progression topography after re-irradiation, in-field (largest proportion within the volume), distant (>2 cm outside the volume or in another anatomical region), or marginal (largest proportion within 2 cm and in the same anatomical region) relative to the irradiated planning target volume; locally controlled survival, defined as the time from randomisation to local (in-field or marginal) progression or death; occurrence of radionecrosis; long-term survival (overall survival >1 year); quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-15 Palliative questionnaire); and the role of diffusion, perfusion, and FLAIR-MRI sequences. Long-term survival, quality of life, and the role of diffusion, perfusion, and FLAIR-MRI sequences will be reported elsewhere.

Statistical analysis

Sample size derivation used the primary endpoint of progression-free survival. For recurrent glioblastoma of 1–6 cm, a 30% 6-month progression-free survival was expected in the control group.[13,17] We hypothesised that FET-PET-based re-irradiation would increase progression-free survival to 45%. Assuming an exponential progression-free survival distribution, this corresponded to a hazard ratio (HR) of 0·667 for the experimental group versus the control group. With a

one-sided significance level of α=10% for the log-rank test and 90% power, 200 patients (177 progression-free survival events) were required to detect a benefit in the experimental group, accounting for two interim analyses. Both interim analyses were prospectively cancelled (appendix p 122).

The patient cohort receiving the FET-tracer for screening was defined as the pharmacovigilance population. The per-protocol population included patients who initiated treatment per their assigned group and analyses were performed by randomly assigned group. The safety population comprised all patients who started re-irradiation and analyses were performed in the group in which re-irradiation had been started.

Endpoints of oncological efficacy were analysed in the per-protocol population. Surviving patients without progression or unplanned antitumour therapy at last follow-up were censored for progression-free survival on the day of the last MRI. Patients without in-field or marginal progression who were alive at last follow-up were censored for locally controlled survival on the day of last MRI. For patients not known to have died, overall survival was censored on the last date known alive. For five deceased patients whose date of death could not be obtained, the date of the last visit was used as date of death.

Progression-free survival, overall survival, and locally controlled survival were estimated using the Kaplan–Meier method; two-sided 95% CIs used Greenwood's log–log transformation. Follow-up was calculated from censored observations because planned reverse Kaplan–Meier curves did not reach medians.

The primary comparison between treatment groups for progression-free survival was performed using the one-sided log-rank test with a significance level of α=10%, stratified by randomisation stratification factors (appendix p 2). The HR for the experimental group versus the control group and its two-sided 95% CI was estimated using a multivariable proportional hazards model, adjusting for stratification factors. Visual inspection confirmed the proportional hazards assumption. Secondary descriptive analyses used two-sided α=5%. Descriptive analyses were performed for gross tumour volumes and their overlap, including the Dice similarity coefficient, as well as for progression and radionecrosis topography. Prespecified exploratory analyses investigated the effect of the different volumes on locally controlled survival, progression-free survival, and overall survival using a multivariable fractional polynomial interaction approach. These included the size of the gross tumour volume on PET that did not overlap with the gross tumour volume on MRI and the percentage of the non-randomly assigned gross tumour volume (gross tumour volume on MRI in the FET-PET group and gross tumour volume on PET in the CE-T1MRI group) receiving 30 Gy or more or 37 Gy or

	FET-PET group (n=100)	CE-T1MRI group (n=100)
Age, years		
Mean	59·3 (11·0)	60·6 (9·9)
Median	59·5 (53·0–67·0)	60·5 (55·0–67·0)
Sex		
Female	45 (45%)	40 (40%)
Male	55 (55%)	60 (60%)
Median height, cm	170·5 (165·0–179·5)	172·0 (166·0–178·5)
Median weight, kg	75·0 (65·0–85·0)	75·5 (67·0–86·0)
Karnofsky performance status		
90–100% (ECOG 0)	52 (52%)	49 (49%)
70–80% (ECOG 1)	48 (48%)	51 (51%)
Time from the first radiotherapy, months		
Median	11·6 (7·7–21·2)	12·0 (8·2–19·4)
≤14	58 (58%)	61 (61%)
>14	42 (42%)	39 (39%)
Histology of pre-irradiated tumour		
Glioblastoma WHO grade IV	90 (90%)	93 (93%)
Anaplastic astrocytoma WHO grade III	5 (5%)	4 (4%)
Anaplastic oligodendroglioma WHO grade III	1 (1%)	0
Anaplastic oligoastrocytoma WHO grade III	2 (2%)	1 (1%)
Other (WHO grades III or IV)	2 (2%)	2 (2%)
Median full dose applied at previous irradiation, Gy	60·0 (60·0–60·0)	60·0 (60·0–60·0)
Median fraction dose of previous irradiation, Gy	2·0 (2·0–2·0)	2·0 (2·0–2·0)
Previous systemic therapy*		
At least one chemotherapy	96 (96%)	96 (96%)
Temozolomide concomitant to radiotherapy	92 (92%)	92 (92%)
Temozolomide adjuvant (conventional protocol of 5 days in every 28-day cycle)	87 (87%)	89 (89%)
Lomustine	10 (10%)	15 (15%)
Temozolomide (dose dense protocol of 7 days in every 14-day cycle)	6 (6%)	12 (12%)
Procarbazine, lomustine, and vincristine	1 (1%)	1 (1%)
Irinotecan	1 (1%)	0
Other (temozolomide plus lomustine, carmustine, cilengitide)	2 (2%)	2 (2%)
Temozolomide up to seven cycles (one cycle concomitant plus six adjuvant cycles)	69 (69%)	71 (71%)
Temozolomide more than seven cycles	31 (31%)	29 (29%)
Localisation of recurrent glioblastoma*		
Temporal lobe	47 (47%)	50 (50%)
Parietal lobe	42 (42%)	33 (33%)
Frontal lobe	31 (31%)	41 (41%)
Occipital lobe	9 (9%)	11 (11%)
Cerebellum	0	3 (3%)
Brainstem	1 (1%)	0
MGMT status		
Methylated	41 (41%)	41 (41%)
Not methylated	31 (31%)	31 (31%)
Unknown at randomisation	28 (28%)	28 (28%)
Resection of recurrent glioblastoma before re-irradiation	50 (50%)	44 (44%)

(Table 1 continues on next page)

	FET-PET group (n=100)	CE-T1MRI group (n=100)
(Continued from previous page)		
Planned chemotherapy (temozolomide and/or lomustine parallel and/or sequential to re-irradiation)		
No	23 (23%)	25 (25%)
Yes	27 (27%)	25 (25%)
Option not available (before amendment)	50 (50%)	50 (50%)
Gross tumour volume MRI, mL		
Mean	10·5 (11·5)	10·9 (12·2)
Median	6·4 (3·2–13·1)	7·9 (3·0–13·5)
Gross tumour volume PET, mL		
Mean	11·5 (12·3)	10·5 (9·0)
Median	7·8 (3·1–15·1)	8·5 (3·7–13·4)
Focality on MRI		
Unifocal	55 (55%)	42 (42%)
Multifocal	45 (45%)	58 (58%)
Focality on PET		
Unifocal	50 (50%)	43 (43%)
Multifocal	50 (50%)	57 (57%)
Maximum diameter on MRI, mm		
Mean	42·0 (13·4)	43·2 (12·3)
Median	43·0 (33·0–54·5)	46·5 (35·0–52·0)
Gross tumour volume ≤3 cm	20·0 (20%)	18·0 (18%)
Gross tumour volume >3 cm	80·0 (80%)	82·0 (82%)
Maximum diameter on PET, mm		
Mean	42·3 (15·3)	42·4 (13·0)
Median	45·0 (31·0–54·5)	42·0 (32·5–54·5)

Data are mean (SD), median (IQR), or n (%). ECOG=Eastern Cooperative Oncology Group. FET=O-(2-[^{18}F]fluoroethyl)-L-tyrosine. *More than one option was possible.

Table 1: **Demographic and clinical characteristics**

more (appendix pp 129–130). The 6-month progression-free survival and the 12-month locally controlled survival were estimated in post-hoc analyses using the Kaplan–Meier method.

Rates of adverse events and serious adverse events were reported in the pharmacovigilance and safety populations. The toxicity analysis was performed in the safety population, evaluating the highest grade of acute, subacute, and late adverse events per group. Cumulative incidence of any severe side-effect (grade ≥3 or corticosteroid use due to adverse events) was estimated as a function of time from re-irradiation initiation, with death as competing event.

All analyses were prespecified in the protocol and statistical analysis plan (appendix p 116), which were finalised before any data analysis. An independent data safety monitoring committee reviewed adverse events at least annually. Statistical computing used SAS version 9.4, Stata version 14.1, and R version 4.3.1.

Role of the funding source

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

Results

From Nov 22, 2013, to Aug 18, 2021, 271 patients were recruited and screened for eligibility, 200 of whom were randomly assigned at 14 sites between Nov 26, 2013, and Sept 2, 2021, to FET-PET-based (n=100) or CE-T1MRI-based (n=100) target volume definition (figure 1). One site recruited one patient but they were not randomly assigned as they did not fulfil eligibility criteria. Baseline demographic and clinical characteristics showed balanced and comparable cohorts (table 1). 85 (43%) participants were female and 115 (58%) were male. The latest patient follow-up was on Oct 13, 2022. Median follow-up for censored patients was 12·2 months (IQR 6·6–20·7). 98 patients in the FET-PET group and 97 patients in the CE-T1MRI group were treated according to the allocated group per protocol. The safety population consisted of 99 patients per group who started treatment.

Re-irradiation was performed as planned (39 Gy) in 94 (96%) of 98 patients in the FET-PET group and 96 (99%) of 97 patients in the CE-T1MRI group. Radiotherapy was discontinued in five patients in the FET-PET group and two in the CE-T1MRI group. 17 (17%) of 98 patients in the FET-PET group and 15 (15%) of 97 in the CE-T1MRI group received concurrent chemotherapy; sequential chemotherapy was administered in 12 (12%) patients in the FET-PET group and 16 (16%) in the CE-T1MRI group. Corticosteroids were administered to 73 (74%) patients in the FET-PET group and 76 (78%) in the CE-T1MRI group.

After a median follow-up of 4·1 months (IQR 2·3–6·6, six censored patients), median progression-free survival was 4·0 months (95% CI 3·7–5·2; 97 events) in the FET-PET group and 4·9 months (3·7–6·0; 92 events) in the CE-T1MRI group (one-sided stratified log-rank test p=0·98; figure 2A) The adjusted HR for FET-PET versus CE-T1MRI was 1·14 (95% CI 0·85–1·52; p=0·39), with a 6-month progression-free survival of 31% (95% CI 22–40) in the FET-PET group and 38% (29–48) in the CE-T1MRI group.

After a median follow-up of 12·2 months (IQR 6·6–20·7) for censored patients, median overall survival was 9·4 months (95% CI 7·8–11·1; 91 events) in the FET-PET group and 9·0 months (7·6–10·5; 85 events) in the CE-T1MRI group (figure 2B). The adjusted HR for FET-PET versus CE-T1MRI was 1·01 (95% CI 0·75–1·37; p=0·92).

After a median follow-up 6·3 months (IQR 2·3–8·4) for censored patients, the median locally controlled survival was 6·3 months (95% CI 5·1–7·2; 92 events) in the FET-PET group and 6·8 months (6·2–7·3; 84 events) in the CE-T1MRI group (figure 2C). The adjusted HR for FET-PET versus CE-T1MRI was 1·20 (95% CI 0·88–1·62; p=0·25). The local control rate at 12 months was 22% (95% CI 14–31) in the FET-PET group and 20% (12–29) in the CE-T1MRI group. Reasons for censoring are in the appendix (p 3).

Of 60 patients with progression on imaging in the FET-PET group, 27 (45%) had recurrence in-field, 17 (28%) distant, 13 (22%) marginal, and three (5%) in an unknown location. Of 57 patients with progression on imaging in the CE-T1MRI group, 27 (47%) had recurrence in-field, 18 (32%) distant, eight (14%) marginal, and four (7%) in an unknown location. Subsequent therapies at progression are described in the appendix (p 3).

Gross tumour volumes on PET and on MRI were similar in size in both groups (FET-PET: median 7·2 mL [IQR 3·0–15·1] on PET and 6·1 mL [3·2–11·6] on MRI; CE-T1MRI: median 8·5 mL [4·2–14·0] on PET and 8·1 mL [3·0–13·5] on MRI). Median overlapping volume between gross tumour volume on PET and gross tumour volume on MRI was 3·7 mL (IQR 1·3–7·5) and the median non-overlapping volume was 6·6 mL (3·3–16·6). Median Dice similarity coefficient was 0·5 (IQR 0·3–0·6). Gross tumour volume distribution, mean volume, and a schematic illustration of dose distribution are shown in figure 3.

In the FET-PET group, the volume of the gross tumour volume on PET non-overlapping with the gross tumour volume on MRI was median 3·2 mL (IQR 1·3–8·1), and the gross tumour volume on MRI non-overlapping with the gross tumour volume on PET was median 2·7 mL (0·9–4·7). In the CE-T1MRI group, these volumes were 3·6 mL (1·8–7·0) and 2·4 mL (1·2–5·9), respectively.

In prespecified exploratory analyses, the size of the gross tumour volume on PET that did not overlap with the gross tumour volume on MRI had no significant influence on the difference between groups in locally controlled survival (p=0·14), progression-free survival (p=0·64), or overall survival (p=0·19).

In the FET-PET group, a mean of 93·2% (SD 13·6) of the non-target gross tumour volume on MRI was found within the 30 Gy-isodose and 87·7% (17·7) within the 37 Gy-isodose according to the treatment plan (missing, n=1). In the CE-T1MRI group, 93·6% (14·5) of the non-target gross tumour volume on PET was located within the 30 Gy-isodose and 89·7% (15·9) within the 37 Gy-isodose. In 93 (96%) of 97 patients in the CE-T1MRI group, more than 50·0% of the gross tumour volume on PET was covered by the 95% (37 Gy) isodose of the MRI-based plan and thus received the planned therapeutic dose. In only two (2%) of 97 patients, less than 20·0% of the gross tumour volume on PET was covered by the 95% isodose of the MRI-based plan.

Prespecified exploratory analyses found no significant influence of the percentage of gross tumour volume on MRI receiving 30 or more Gy or 37 or more Gy in the FET-PET group, nor of the corresponding percentage of gross tumour volume on PET in the CE-T1MRI group on the difference between groups in locally controlled survival, progression-free survival, or overall survival (data not shown).

In the pharmacovigilance population (239 screened patients), within 7 days after FET-PET (pharmacovigilance

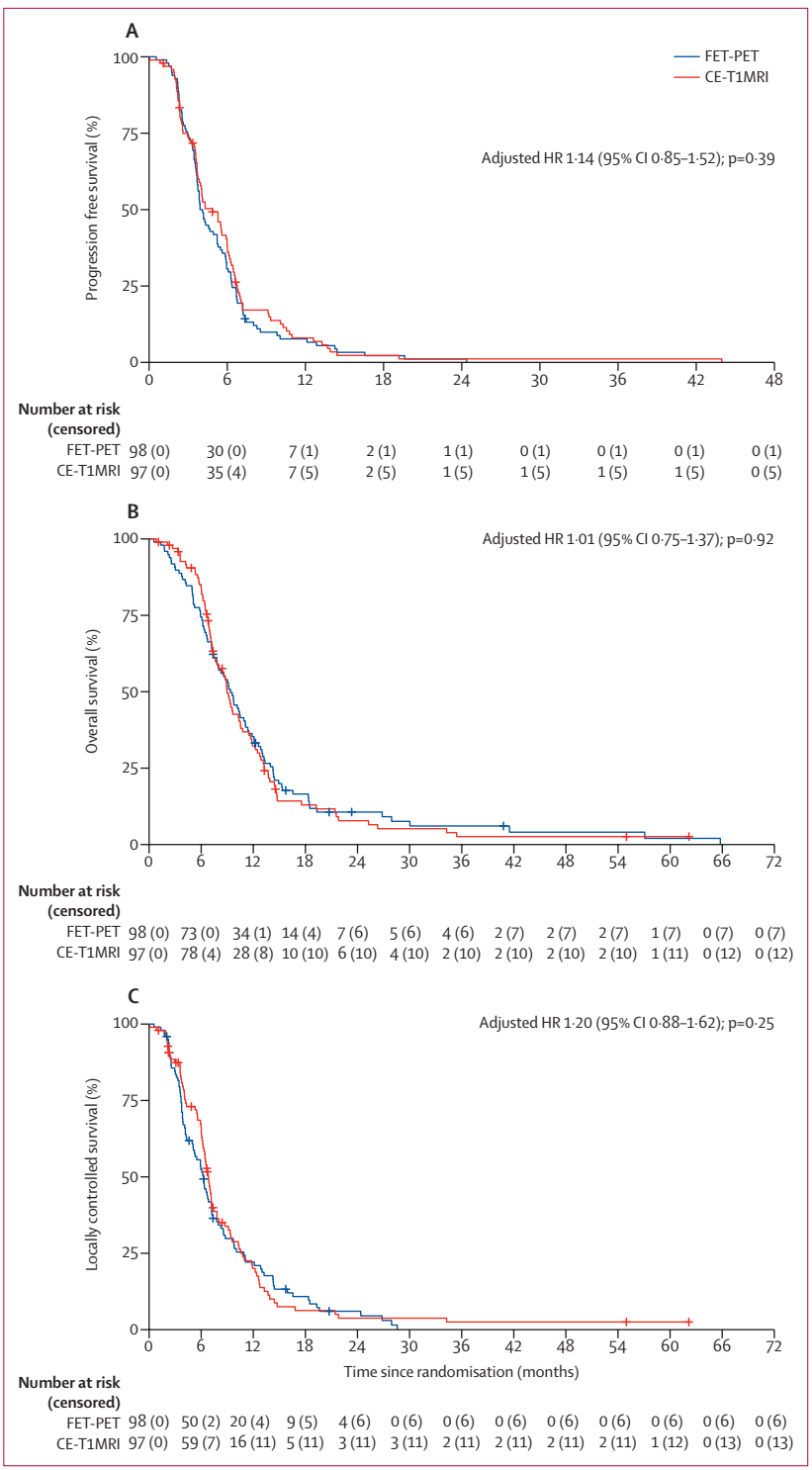

***Figure 2*: Progression-free survival, overall survival, and locally controlled survival**
(A) Progression-free survival in the per-protocol population. (B) Overall survival in the per-protocol population. (C) Locally controlled survival in the per-protocol population. CE-T1MRI=contrast-enhanced T1-weighted MRI. FET=O-(2-[^{18}F]fluoroethyl)-L-tyrosine. HR=hazard ratio.

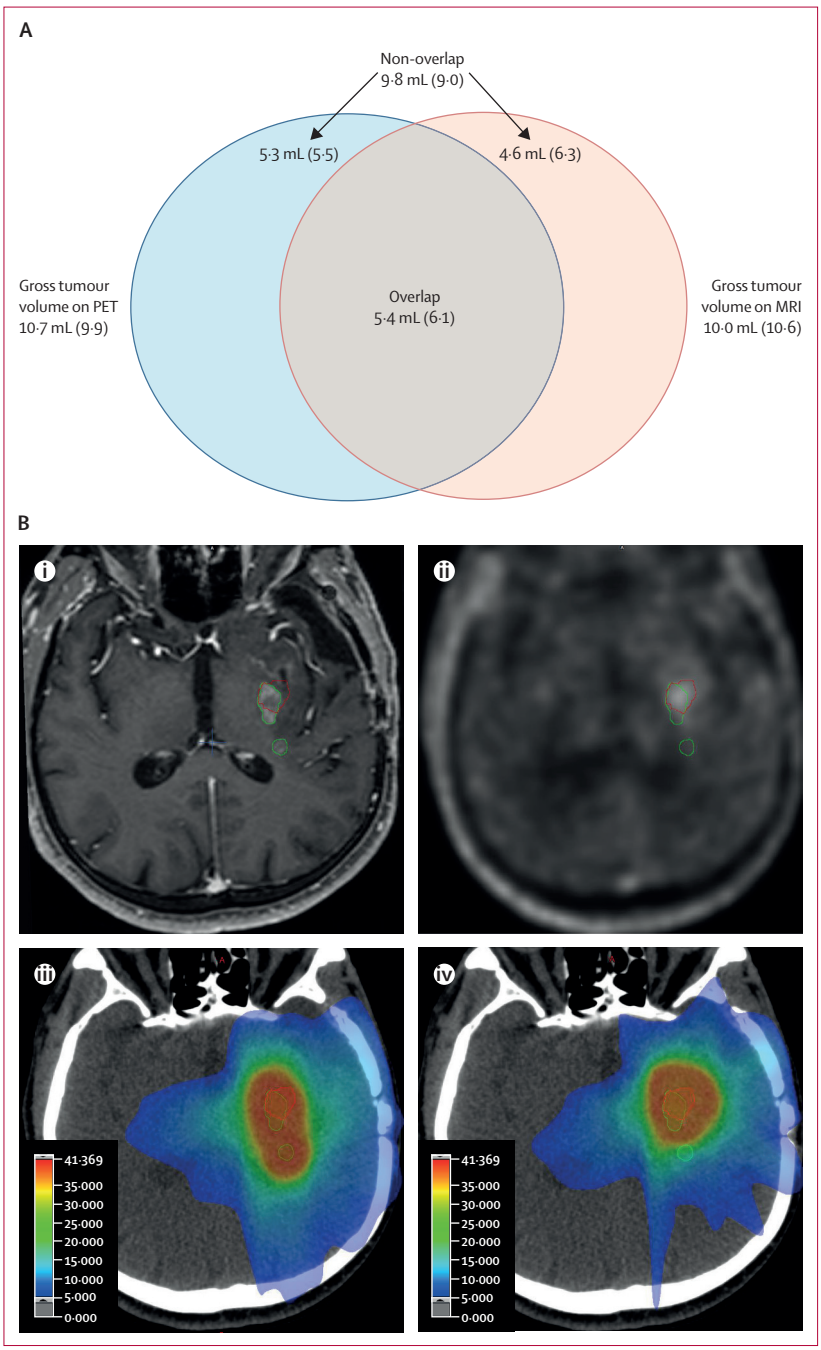

Figure 3: **Spatial relationship of PET-based and MRI-based gross tumour volumes**
(A) Venn diagram of the overlapping and non-overlapping volumes (mean [SD]) between the PET-based and MRI-based gross tumour volumes in the per-protocol population. For descriptive purposes, this figure reports mean (SD) values, while the main text reports median (IQR) values. (B) Schematic illustration of contours and dose distribution for (i) axial CE-T1MRI for radiotherapy planning, (ii) axial FET-PET for radiotherapy planning, (iii) planning CT of CE-T1MRI-based radiotherapy plan, and (iv) axial planning CT of FET-PET-based radiotherapy plan. Green contour shows gross tumour volume on MRI, red contour shows gross tumour volume on PET, orange colour shows high dose, blue colour shows low dose (see colourwash scale). CE-T1MRI=contrast-enhanced T1-weighted MRI. FET=O-(2-[^{18}F]fluoroethyl)-L-tyrosine.

time span), there were 13 adverse events in nine patients and five serious adverse events in three patients, including reduced vigilance, increased intracranial pressure symptoms, focal seizure, hypocortisolism and food poisoning. No event was attributed to FET administration.

The cumulative incidence of any severe adverse event grade 3 or worse in the safety population is in the appendix (p 4). 12 (12%) of 99 patients in the FET-PET group and 14 (14%) of 99 in the CE-T1MRI group had acute or subacute severe adverse events; 20 (20%) patients in the FET-PET group and 16 (16%) in the CE-T1MRI group had a late severe adverse events (table 2). Only one patient in the FET-PET group had interrupted treatment because of adverse events.

Corticosteroid medication for treatment-related adverse events was also considered a severe adverse event, even in the absence of grade 3 or worse adverse events. Eight (8%) of 99 patients re-irradiated based on FET-PET and ten (10%) of 99 patients re-irradiated based on CE-T1MRI imaging received corticosteroids for acute toxicity; ten (10%) patients re-irradiated based on FET-PET and nine (9%) patients re-irradiated based on CE-T1MRI received corticosteroids for late adverse events.

15 (15%) of 99 patients in the FET-PET group and 15 (15%) of 99 in the CE-T1MRI group had a serious adverse event during or up to 30 days after re-irradiation. After 30 days, serious adverse events possibly related to re-irradiation occurred in ten (10%) of 97 surviving patients in the FET-PET group and in 18 (19%) of 96 surviving patients in the CE-T1MRI group. There were no treatment-related deaths (appendix p 5).

All-grade radionecrosis was observed in 25 (25%) of 99 patients in the FET-PET group and 21 (21%) of 99 patients in the CE-T1MRI group. Nine (9%) patients the FET-PET group and nine (9%) in the CE-T1MRI group had early (within 90 days after start of re-irradiation) radionecrosis; 21 (21%) patients in the FET-PET group and 14 (14%) in the CE-T1MRI group had late radionecrosis. Bevacizumab was administered for radionecrosis in nine (9%) patients in the FET-PET group and six (6%) in the CE-T1MRI group. Grade 3–4 radionecrosis occurred in eight (8%) patients in the FET-PET group and seven (7%) in the CE-T1MRI group. In the patients with grade 3 or worse radionecrosis, the diagnosis of radionecrosis was confirmed through biopsy in 13 patients and resection in one patient, while one patient had no histological confirmation.

Discussion

To our knowledge, this is the first study to show the feasibility of, and directly compare, a solely FET-PET-based target volume delineation with conventional CE-T1MRI-guided planning for the re-irradiation of patients with recurrent glioblastoma. This trial answers a clinically relevant question in radiation oncology.

FET-PET-guided radiotherapy was not shown to improve oncological outcomes in recurrent glioblastoma. Thus, CE-T1MRI remains the preferred delineation method as supported by RTOG 1205.[18] Nevertheless, PET imaging has a complementary role to MRI in diagnosing recurrent glioblastoma and thereby adds value in the challenging context of treatment of this disease.[3]

Re-irradiation for recurrent glioblastoma requires highly precise dose delivery to achieve therapeutic benefits while maintaining acceptable toxicity levels. Technical advances, such as stereotactic and intensity-modulated radiotherapy, have substantially increased the number of eligible patients, establishing re-irradiation as a treatment option in recurrent glioblastoma.[19–21]

This study confirms, in a large patient cohort, a considerable spatial mismatch between gross tumour volumes delineated on FET-PET and CE-T1MRI, consistent with findings from the GLIAA pilot trial[12] and other retrospective analyses.[9–11] However, unlike previous studies, the delineated volumes were similar in size. An explanation for this discrepancy lies in methodological differences in PET-based tumour delineation, in particular the threshold chosen to distinguish tumour tissue from background activity. In this study, we recommended a threshold for the tumour-to-background ratio of 1·8 for FET-PET, as opposed to 1·6–1·7 used in earlier and ongoing investigations, which mainly included gliomas that were not pre-irradiated.[9–11,22] The chosen threshold, still consistent with current guidelines,[23] aimed to ensure, to the best of our knowledge, the presence of active tumour tissue in the target volume following initial radiotherapy and reduce the risk of toxicity from unnecessarily large treatment areas. Nonetheless, additional analyses are planned, investigating the PET volume at a lower threshold for the tumour-to-background ratio of 1·6 and the corresponding recurrence pattern.

Given the high specificity of FET-PET to detect recurrent glioblastomas, it seems paradoxical that FET-PET-based radiotherapy did not improve patient outcome. However, our results show that gross tumour volume on PET and gross tumour volume on MRI were located close to each other. Moreover, the planning target volume was defined with a 5 mm margin to gross tumour volume and the prescribed dose to the planning target volume exceeded current recommendations of the European Society for Radiotherapy and Oncology and the European Association of Neuro-Oncology (ESTRO–EANO) for re-irradiation of glioblastoma.[19] Thus, even in a highly conformal treatment plan, a therapeutically active dose might have been delivered even outside the planning target volume. There is increasing evidence that local tumour control can be achieved in spite of a heterogeneous dose distribution.[24] This effect could be one explanation for our results. One might also hypothesise that tumour segments that are both MRI-positive and PET-positive represent the most aggressive areas and might be the targets with the highest prognostic relevance.

	FET-PET group (n=99)			CE-T1MRI group (n=99)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Acute and subacute adverse events						
Alopecia	40 (40%)	0	0	31 (31%)	0	0
Fatigue	18 (18%)	1 (1%)	0	26 (26%)	1 (1%)	0
Headache	13 (13%)	0	0	11 (11%)	1 (1%)	0
Radiodermatitis	11 (11%)	0	0	13 (13%)	0	0
Corticosteroid medication with indication toxicity	0	8 (8%)	0	0	10 (10%)	0
Hemiparesis	0	3 (3%)	0	0	0	0
Radionecrosis	0	1 (1%)	0	0	1 (1%)	0
Generalised epileptic seizures	0	0	0	0	1 (1%)	0
Focal epileptic seizures	0	1 (1%)	0	0	0	0
Difficulty concentrating	0	1 (1%)	0	0	0	0
Cognitive disorder	0	1 (1%)	0	0	0	0
Leukoencephalopathy	0	0	0	0	1 (1%)	0
Late adverse events						
Alopecia	25 (25%)	0	0	20 (20%)	0	0
Radionecrosis	14 (14%)	6 (6%)	1 (1%)	8 (8%)	5 (5%)	1 (1%)
Fatigue	14 (14%)	0	0	13 (13%)	1 (1%)	0
Corticosteroid medication with indication toxicity	0	10 (10%)	0	0	9 (9%)	0
Hemiparesis	0	2 (2%)	0	0	1 (1%)	0
Cognitive disorder	0	2 (2%)	0	0	0	0
Focal epileptic seizures	0	1 (1%)	0	0	0	0
Aphasia	0	1 (1%)	0	0	0	0
Hearing loss	0	1 (1%)	0	0	0	0
Personality disorder	0	1 (1%)	0	0	0	0

Grade 1–2 adverse events are reported if they occurred in more than 10% of patients. Acute adverse events were within 90 days following re-irradiation. Late adverse events were after 90 days following re-irradiation.

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

The inclusion criteria, imaging parameters, radiotherapy planning methods, and follow-up procedures in the GLIAA trial fully comply with the ESTRO–EANO guidelines.[19] The observed median progression-free survival of 4·0–4·9 months generally aligns with established oncological benchmarks.[18–20] Inclusion criteria in the GLIAA trial were similar to the phase 2 RTOG 1205 trial.[18] However, in the current study, patients without macroscopic recurrent glioblastoma were not included, whereas in RTOG 1205, 63·5% of patients had undergone recent gross tumour resection. The effect of recent partial resection on treatment effect or outcome will be published subsequently in an analysis evaluating prognostic factors in the whole cohort. Furthermore, RTOG 1205 used the MacDonald criteria for progression assessment, whereas GLIAA used the RANO criteria, which more formally integrate clinical status and steroid use. These differences, alongside the challenges in image interpretation following bevacizumab, might explain the higher progression-free survival of 7·1 months after

re-irradiation and bevacizumab in the RTOG 1205 trial than in this trial.

Median locally controlled survival was 6·3 months in the FET-PET group and 6·8 months in the CE-T1MRI group, with a low rate of marginal recurrences in both groups, suggesting sufficient target coverage. Median overall survival rates were also consistent with those reported in the literature for PET-based re-irradiation of recurrent high-grade glioma, ranging between 7 and 11 months.[11,25–27]

Regarding the generalisability of our findings, it is worth mentioning that the GLIAA trial treated tumours of 1 cm up to 6 cm and also enrolled patients with second or subsequent recurrences as well as patients with relatively early recurrences (6 months after initial treatment). The partially negative selection of the study cohort is further evidenced by the fact that chemotherapy was not recommended in approximately half of eligible patients, primarily due to poor bone marrow reserve or previous progression during chemotherapy. Still, our data show a meaningful outcome for this vulnerable patient population when compared with literature data[20] and thus might support the role of re-irradiation in patients with recurrent glioblastoma.

The applied dose in our trial exceeded the internationally recommended 36 Gy $EQD2_{\alpha/\beta=3\ Gy}$,[19] achieving high local tumour control. The dose was chosen taking the cumulative brain tolerance into consideration.[16] The occurrence of radionecrosis of any grade was thoroughly evaluated based on MRI, FET-PET, and histology and was diagnosed in approximately one-quarter of patients, within the range of rates reported previously.[17,18,20,25–27] All patients could be treated with dexamethasone, bevacizumab, or resection and there were no treatment-related deaths. Overall, the toxicity of re-irradiation was acceptable and similar in both groups. Especially in the era of bevacizumab, radionecrosis has become less concerning. Given the number of in-field failures and the relatively small treatment volumes in this study, a further dose escalation applied together with bevacizumab might be considered in the future.

One limitation of this trial is that not all patients had a histologically confirmed recurrence. However, the trial only included patients with positive FET-PET with a minimum size of 1 cm, making it unlikely that the results are biased by the inclusion of patients without recurrent glioblastoma. Other potential limitations arise from the imaging methods used for treatment planning in both groups. In the CE-T1MRI group, only contrast-enhancing lesions and not FLAIR alterations, which are known to contain glioma cell infiltrates,[28] were considered. However, signal abnormality in FLAIR is relatively unspecific after initial radiotherapy.[29] Other MRI sequences, such as diffusion, have also been shown not to predict well the location of further tumour progression.[12] Expanding the gross tumour volume to include all suspicious areas in multiparametric MRI would have led to larger target volumes and higher toxicity. In the FET-PET group, static PET was used for delineation, although the combination of static and dynamic FET-PET parameters has been shown to provide higher diagnostic accuracy in distinguishing recurrent glioblastoma from treatment-related changes.[30] However, the use of dynamic FET-PET to generate parametric images for definition of target volumes is not well established and the longer acquisition times can cause movement artefacts, reducing image quality.

Another important consideration is the challenge in confirming the diagnosis of tumour progression or treatment-related changes and radionecrosis. After re-irradiation of glioblastoma, a complex interplay between viable tumour tissue and therapy-induced changes most often occurs, making differential diagnosis particularly difficult. In this trial, we used all available diagnostic modalities, including serial multiparametric MRI under therapeutic challenge with dexamethasone, FET-PET, and histological confirmation. However, we acknowledge the inherent limitations of each of these approaches and the unavoidable bias introduced by using imaging methods both for the definition of target volumes and for the diagnosis of recurrence. Last, the trial was designed before the newest adaptations of the WHO classification, therefore the isocitrate dehydrogenase mutation was not reported.

In conclusion, the current trial is, to our knowledge, the first randomised trial assessing the oncological efficacy of FET-PET versus CE-T1MRI-based re-irradiation in patients with recurrent glioblastoma. The study showed the safety of the FET-PET examination and implemented a standardised method for FET-PET-based target volume definition for recurrent glioblastoma, which leads to similar oncological outcomes as the traditional MRI-based treatment. Since only PET-positive patients were included, the results of this trial do not question the role FET-PET has in the differential diagnosis of recurrent glioblastoma from post-therapeutic changes. These prospective data provide valuable information on the oncological efficacy and side-effect profile of cerebral re-irradiation and support the radiotherapy process in recurrent glioblastoma.

Contributors

A-LG and WAW conceived the study concept and initiated the study design together with UN, IM, K-JL, and BGB. TS-J helped with the implementation. A-LG, WAW, UN, and TS-J worked on the funding acquisition. A-LG is the grant holder. EG provided statistical expertise. MM, RW, and IP were involved in quality assurance. Data collection was performed by IP, MM, TS-J, RW, IM, UW, MN, FP, LK, FAG, MMS, IS, DB, CP, SS, TB, BH, BJK, IFC, JB, PTM, and HU. A-LG, IP, WAW, and EG analysed and interpreted the data. IP, A-LG, and WAW wrote the manuscript (with the main draft written by IP). A-LG, IP, and EG have accessed and verified the data. All authors reviewed the manuscript, made the decision to submit the manuscript for publication, and assured the completeness and accuracy of the data and analyses and of the fidelity of this report to the trial protocol. All

authors approved the final manuscript and could have access to the data on request.

Declaration of interests

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Data sharing

From publication of the main results, de-identified data collected for the GLIAA trial and dictionaries can be made available with investigator support for other research projects on the approval by the study group and ethics committee. For this, please contact the principal investigator of the trial (A-LG, anca.grosu@uniklinik-freiburg.de) with your project proposal.

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