

BMJ Open Investigating survival, quality of life and cognition in PROton versus photon therapy for *IDH*-mutated diffuse grade 2 and 3 GLIomas (PRO-GLIO): a randomised controlled trial in Norway and Sweden

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ABSTRACT

Introduction The use of proton therapy increases globally despite a lack of randomised controlled trials demonstrating its efficacy and safety. Proton therapy enables sparing of non-neoplastic tissue from radiation. This is principally beneficial and holds promise of reduced long-term side effects. However, the sparing of seemingly non-cancerous tissue is not necessarily positive for isocitrate dehydrogenase (*IDH*)-mutated diffuse gliomas grade 2–3, which have a diffuse growth pattern. With their relatively good prognosis, yet incurable nature, therapy needs to be delicately balanced to achieve a maximal survival benefit combined with an optimised quality of life.

Methods and analysis PRO-GLIO (PROton versus photon therapy in *IDH*-mutated diffuse grade 2 and 3 GLIomas) is an open-label, multicentre, randomised phase III non-inferiority study. 224 patients aged 18–65 years with *IDH*-mutated diffuse gliomas grade 2–3 from Norway and Sweden will be randomised 1:1 to radiotherapy delivered with protons (experimental arm) or photons (standard arm). First intervention-free survival at 2 years is the primary endpoint. Key secondary endpoints are fatigue and cognitive impairment, both at 2 years. Additional secondary outcomes include several survival measures, health-related quality of life parameters and health economy endpoints.

Ethics and dissemination To implement proton therapy as part of standard of care for patients with *IDH*-mutated

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ PRO-GLIO (PROton versus photon therapy in *IDH*-mutated diffuse grade 2 and 3 GLIomas) is the largest randomised controlled trial to date comparing photon versus proton therapy for patients with *IDH*-mutated diffuse glioma grades 2 and 3.
- ⇒ The number and broadness of secondary and exploratory endpoints—including subjective patient-reported outcome measures based and objective healthcare professional evaluated—enable a holistic evaluation of treatment outcomes and needs.
- ⇒ PRO-GLIO has a very long-term follow-up of 15 years and will thereby disclose the true disease course over all these years.
- ⇒ PRO-GLIO is a comprehensive study also involving patients' next of kin and a longitudinal qualitative study for a subset of patients.
- ⇒ Blinding of patients or healthcare providers is not possible.

diffuse gliomas grade 2–3, it should be deemed safe. With its randomised controlled design testing proton versus photon therapy, PRO-GLIO will provide important information for this patient population concerning safety, cognition, fatigue and other quality of life parameters. As proton therapy is considerably more costly than its

photon counterpart, cost-effectiveness will also be evaluated. PRO-GLIO is approved by ethical committees in Norway (Regional Committee for Medical & Health Research Ethics) and Sweden (The Swedish Ethical Review Authority) and patient inclusion has commenced. Trial results will be published in international peer-reviewed journals, relevant conferences, national and international meetings and expert forums.

Trial registration number ClinicalTrials.gov Registry (NCT05190172).

INTRODUCTION

Diffuse gliomas represent one of the most prevalent primary brain tumour entities and are graded according to the 2021 WHO Classification of Tumors of the Central Nervous System.¹ Their diffuse growth pattern is the defining characteristic rendering these neoplasms incurable diseases, although prognosis varies greatly. This study focuses on diffuse grade 2–3 gliomas, that is, astrocytomas and oligodendrogliomas, which by definition harbour an isocitrate dehydrogenase (*IDH*)-mutation. The presence of such an *IDH*-mutation is prognostically beneficial and conveys more prognostic information than histopathological grading.^{2,3} Patients with these gliomas have a median overall survival (OS) of around 10 years^{4–6}; patients with oligodendroglioma grade 2 have the longest expected life span and those with astrocytoma grade 3 have a relatively poorer prognosis.

Therapies for diffuse gliomas are multimodal including surgery, radiotherapy and chemotherapy.^{7–13} Radiotherapy delivered with photon therapy techniques has in the past decades become more precise, enabling good coverage of the radiotherapy target volume while minimising radiation dose to radiotherapeutic organs at risk (OARs). However, normal brain will inevitably receive some irradiation which may result in short-time and long-time sequelae; short-time sequelae often resolve completely, whereas long-term sequelae are irreversible and may progress with time. One of the most devastating late side effects from radiotherapy is cognitive impairment, which may include deficits in psychomotor functioning, attention, learning, memory and executive functions. Further, these difficulties affect societal participation including the ability to return to work and quality of life (QoL).^{14,15} Fatigue is another important multidimensional concept, which impacts QoL, and is a common side effect from anti-cancer treatment including radiotherapy.^{16,17} Patients diagnosed with *IDH*-mutated diffuse gliomas grade 2–3 are often young with great responsibilities in family life and at work, making them vulnerable to cognitive impairment and decreased QoL.

During the past decade, the use of proton therapy has rapidly increased globally.¹⁸ The main advantage of proton therapy is its ability to deposit most of its energy at a specified depth in the patient, that is, the characteristic Bragg peak. Theoretically, with the resultant sparing of surrounding healthy tissue from radiation dose, proton therapy will lead to diminished treatment-related toxicity. Further, the nature of diffuse gliomas poses a potential problem for proton therapy. As their infiltrative growth pattern is difficult to visualise by present-day imaging,

an approximation is necessary when defining the radiotherapy target volume. This might be problematic if tumour-infiltrated tissue surrounding the target volume receives a lower radiation dose with proton therapy, as the endeavour to improve QoL might lead to poorer patient survival. Several retrospective observational studies^{19–21} and a few small prospective uncontrolled, non-randomised studies^{22,23} have shown proton therapy to be a safe and potentially advantageous treatment strategy compared with photon-based therapy in various brain tumours. Patients reported in these studies were probably selected; hence, randomised controlled trials are needed to disentangle the relative benefits of protons for survival, QoL and health economy.²⁴ An ongoing phase II randomised controlled trial (NRG BN005)²⁵ in the USA started inclusion in 2017. This trial aims at including 120 patients with *IDH*-mutated grade 2 or 3 gliomas and randomise 2:1 to proton or photon therapy. Estimated primary completion date is January 2025.

In summary, the safety and the potential benefits of proton versus photon therapy have not yet been established for diffuse gliomas.²⁶ If survival is non-inferior for these patients, the next question is whether proton therapy is otherwise beneficial compared with photon therapy, as the cost of proton therapy is two to three times higher.²⁷ Hence, quality of survival should be assessed both by objective, clinician-rated and patient-reported outcome measures (PROMs). The PROton versus photon therapy in *IDH*-mutated diffuse grade 2 and 3 GLIOmas (PRO-GLIO) study will investigate all these important perspectives. Extensive data will be collected, from radiotherapy technicalities, survival data and QoL, to experience of next of kin and in-depth qualitative research, enabling a holistic understanding of these patients. The comprehensive and long-term follow-up undertaken in this trial may further increase our knowledge of rehabilitation needs for this patient group. Results from PRO-GLIO will improve the knowledge base on the potential beneficial effects of proton therapy, and we anticipate that the study will contribute to a new standard of care for patients with *IDH*-mutated diffuse glioma grade 2–3, and may also be relevant for patients with other brain neoplasms.

OBJECTIVES

The primary objective of PRO-GLIO is to determine whether proton therapy is non-inferior to photon therapy for 2-year first intervention-free survival (FIFS) in patients with *IDH*-mutated diffuse grade 2–3 gliomas. There are two key secondary objectives: to evaluate and compare fatigue level and cognition 2 years post-radiation for the two radiotherapy modalities. We hypothesise that participants in the experimental proton arm will experience lower fatigue levels compared with standard photon treatment, and that fewer participants in the experimental arm will experience cognitive deficits compared with standard treatment. Other secondary objectives include

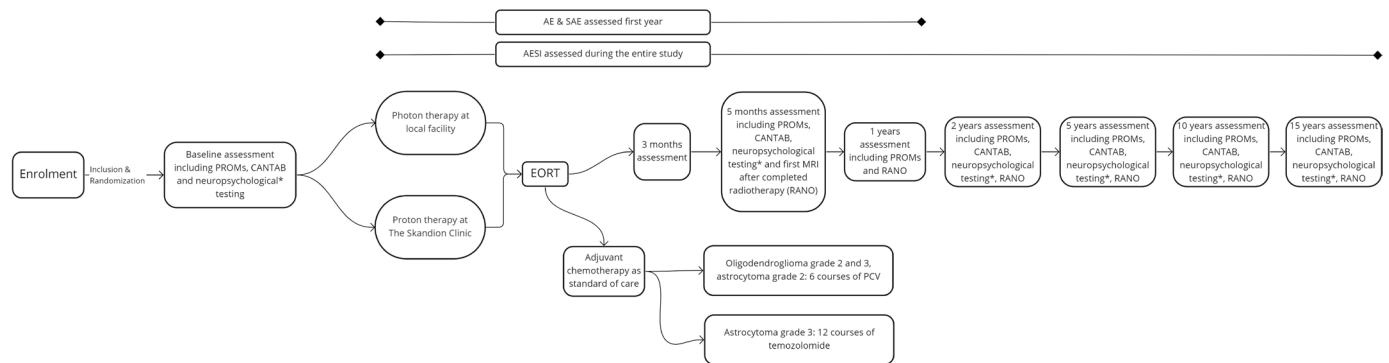


Figure 1 Flow chart. *Norwegian and some Swedish patients only. AE, adverse event; AESI, adverse event of special interest; CANTAB, Cambridge Neuropsychological Test Automated Battery; EORT, end of radiotherapy; PCV, chemotherapy combination of procarbazine, lomustine (CCNU) and vincristine; PROMs, patient-reported outcome measures; RANO, Response Assessment in Neuro-Oncology; SAE, serious adverse event.

several survival variables, PROMs and neuropsychological measures detailed below.

METHODS AND ANALYSIS

Study design

PRO-GLIO is an open-label, multicentre, randomised phase III non-inferiority trial. In total, 224 patients with *IDH*-mutated diffuse gliomas grade 2–3 will be randomised 1:1 to radiotherapy delivered with protons (experimental arm) or photons (standard arm). Patients will be assessed before radiotherapy (baseline) and then reassessed several times during the trial period of 15 years. Inclusion started in January 2022 and is expected to take 3–4 years, that is, total study duration is 19 years, estimated to be completed in 2041 (see figure 1). The primary endpoint analysis is planned when all patients have completed their 2-year assessment. Table 1 displays trial assessments according to Standard Protocol Items: Recommendations for Interventional Trials.²⁸

Study setting

All hospitals responsible for treating these patients in Norway and Sweden have expressed their interest and plan to participate (online supplemental table 1). To optimise treatment and study quality, each participating centre should preferably include five patients or more per year. If a centre includes less than two patients per year, inclusion from this centre may be stopped. The Skandion Clinic is a standalone proton therapy facility in Uppsala, which is owned by seven university hospitals in Sweden. Patients from both Norway and Sweden will be referred to the Skandion Clinic for proton therapy. Norwegian patients allocated to protons will have their radiotherapy planning in a Swedish centre and treatment at the Skandion Clinic; however, target volume and OAR delineation will be performed by oncologists at the patients' Norwegian hospital. Swedish proton patients will have all planning procedures performed at their local facility, whereas treatment is administered at the Skandion Clinic. As of today, there is no proton therapy facility in Norway, but two centres are planned

to open in 2024. When these centres open, Norwegian patients will be treated there. Photon therapy will be administered at the patients' local facilities. All assessments will be conducted at local facilities, with the exception of PROMs and cognitive screening, which will be completed electronically. For participants in the qualitative substudy, interviews will be conducted mainly at Oslo University Hospital (OUH).

Participants

Patients with diffuse *IDH*-mutated grade 2–3 gliomas and 18–65 years old with an indication for radiotherapy, based on tumour board discussions, are included. Eligible participants will be screened when referred to each facility's oncology clinic. Local principal investigators and their teams will provide patients with study information and signed informed consent will be obtained for patients willing to participate. Box 1 displays the eligibility criteria. In the next protocol version, an additional criterion will be added: all participants must be fluent in Norwegian or Swedish. The intention was to exclude patients when more than 2 months had elapsed from baseline to start of radiotherapy. However, this exclusion criterion will be removed in the next protocol version, as it is not possible to assess upfront. All patients will be invited to choose a next of kin who will be asked to participate in a next of kin substudy, after providing written informed consent (see online supplemental file for example). Sociodemographic variables will be recorded for all participants, including age, sex, family information, educational level, income, work status and work ability.

Patient and public involvement

Representatives from the Norwegian and Swedish user organisations are involved in PRO-GLIO, contributing to the study design, choice of outcomes, planning and conducting qualitative substudies and writing of the protocol. Further, a user representative is a member in the Study Steering Committee. Results from this trial will be shared with members of relevant user organisations.



Table 1 SPIRIT table

Study period	Screening -60dM1D1	Baseline -14dM1D1	Intervention	End of radiotherapy	3 months post-irradiation	5 months post-irradiation	1 year post-irradiation	2, 5, 10 and 15 years post-irradiation
Enrolment								
Eligibility screen	X							
Informed consent	X							
Allocation	X*							
Interventions								
Radiotherapy		X						
Assessments								
Physical examination	(X)†	X		X	X	X	X	
Neurological evaluation: NANO score	(X)†	X		X	X	X	X	X
General condition: ECOG status, KPS score	X	X		X	X	X	X	X
PROMs		X			X	X	X	X
Web-based cognitive screening: CANTAB		X			X	X		X
Neuropsychological testing‡		X‡			X‡	X‡		X‡
Radiological assessment: RANO						X	X	X
Basal endocrinological status	(X)†	X			X	X	X	X
Concomitant medication (eg, corticosteroid and AED dose)	(X)†	X		X	X	X	X	X
Epilepsy/seizure control	(X)†	X		X	X	X	X	X
AESI		X		X	X	X	X	X
AE and SAE		X		X	X	X	X	X

*Allocation after the patient is deemed eligible for inclusion and signed informed consent form is collected.
 †Optional at enrolment, repeated at baseline if > 14 days to start of radiotherapy.
 ‡Norwegian and some Swedish patients only.
 AE, adverse event; AED, anti-epileptic drug; AESI, adverse event of special interest; CANTAB, CAbridge Neuropsychological Test Automated Battery; -14dM1D1, maximum 14 days prior to radiotherapy; -60dM1D1, maximum 60 days prior to radiotherapy; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; NANO, Neurological Assessment in Neuro-Oncology; PROMs, patient-reported outcome measures; RANO, Response Assessment in Neuro-Oncology; SAE, serious adverse event; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

Box 1 Eligibility criteria

Inclusion criteria

- ⇒ Patients must be 18–65 years old at the day of consenting.
- ⇒ Isocitrate dehydrogenase (*IDH*)-mutated astrocytoma grade 2 or 3, or oligodendroglioma grade 2 or 3, according to WHO criteria of 2021.
- ⇒ Indication for radiotherapy.
- ⇒ WHO/Eastern Cooperative Oncology Group performance status 0–2.
- ⇒ Ability to undergo MRI.
- ⇒ No significant contrast-enhancing tumour at the time of randomisation. In recurrence patients, no contrast enhancement is allowed unless a new biopsy confirms the diagnosis of *IDH*-mutated astrocytoma grade 2 or 3, or oligodendroglioma grade 2 or 3.
- ⇒ Ability and willingness to travel to the Skandion Clinic for proton therapy if randomised to the proton therapy arm.
- ⇒ Women of childbearing potential must agree to use an effective method of contraception during radiotherapy, chemotherapy and 1 year after completion of chemotherapy. Pregnancy is not an ineligibility criterion if radiotherapy is indicated and cannot be postponed.
- ⇒ Ability to understand the information about the study and included treatment.
- ⇒ Signed informed consent.

Exclusion criteria

- ⇒ Prior treatment (except surgery) for diffuse glioma.
- ⇒ Concomitant or previous malignancies. Exceptions are adequately treated basal cell carcinoma or squamous cell carcinoma of the skin, or in situ carcinoma of the cervix uteri with a follow-up time of at least 3 years, or other previous malignancies with a disease-free interval of at least 5 years.
- ⇒ Known cyclin-dependent kinase inhibitor 2 A/B homozygous deletion.
- ⇒ Presence of any medical, psychological, familial, sociological or geographical characteristic that might impair patient compliance for study protocol procedures including follow-up.
- ⇒ Body weight >150 kg.

Randomisation

Based on the stratification parameters tumour grade (2 vs 3), histology (astrocytoma vs oligodendroglioma) and study site, participants will be allocated to the experimental proton arm or the standard photon arm according to a randomised allocation list with random block sizes prepared by the study statistician (no need for independent statistician as PRO-GLIO is an open-label study). The list is uploaded to the electronic case report form system (eCRF) Viedoc,²⁹ and patient allocation is revealed only when the participant is deemed eligible and ready for randomisation, ensuring the blinding of study personnel during the randomisation process.

Interventions

The study-related intervention in PRO-GLIO is radiotherapy delivered with protons (experimental arm) compared with photons (standard arm) (see [figure 2](#) and [table 2](#)). Every effort will be made to keep radiation doses as low as reasonably achievable to OARs even if OAR constraints are met (online supplemental tables 2 and 3). Precise delineation of target volumes and OARs are

important to achieve adequate dose to the radiotherapy target volume, and at the same time avoid unnecessary dose to critical structures. Target volume definition is inherently difficult for diffuse gliomas and subjective considerations might lead to interobserver variation for target volume delineations, OAR delineation and dose planning. To harmonise target volume delineations, a dummy run procedure for each centre is mandatory before initiation of patient inclusion. In the dummy run, each centre should delineate target volumes and OARs in the same case and perform dose planning based on a given structure set.

Concomitant chemotherapy is not recommended in Norwegian or Swedish national guidelines. As radiotherapy is the only study-related treatment, participants will receive standard of care treatment after completing radiotherapy. This includes standard post-irradiation chemotherapy unless contraindicated. Patients with anaplastic astrocytoma are scheduled to receive 12 temozolomide courses, whereas participants with the three other diagnoses will receive PCV courses (chemotherapy combination of procarbazine, lomustine (CCNU) and vincristine) aiming at six cycles. For some of the latter patients, temozolomide will be preferred over PCV. As this is an incurable disease and follow-up lasts 15 years, a significant number of patients are expected to progress during the follow-up period and these will receive recurrence treatment as per national guidelines. Most patients are expected to cope well during radiotherapy. However, side effects will be monitored closely. In the unlikely event that a patient's health in any way deteriorates during treatment, an investigator will evaluate whether treatment should be adjusted or stopped. Further, if a patient is concurrently affected by any other serious medical condition, a responsible investigator may decide to end follow-up if considered best for the patient. Patients are allowed to withdraw from the study at any time. A formal safety interim analysis will not be performed. Blinding of patients or healthcare providers is not possible.

Outcomes

Outcomes will be assessed at end of radiotherapy, 3 and 5 months and at 1, 2, 5, 10 and 15 years post-irradiary ([table 1](#)).

Primary outcome

FIFS is defined as the number of months from date of start of radiotherapy to the date of first antineoplastic therapy not part of primary treatment or death, this includes salvage surgery. FIFS occurrence at 2 years was chosen as the primary outcome because progression-free survival (PFS), as defined by Response Assessment in Neuro-Oncology (RANO) criteria, is a crude measure, and antineoplastic treatment might be initiated before PFS is reached. Pseudoprogression may also be mistaken as progression and might even have different characteristics in patients treated with proton therapy compared with those who have received photon therapy.³⁰

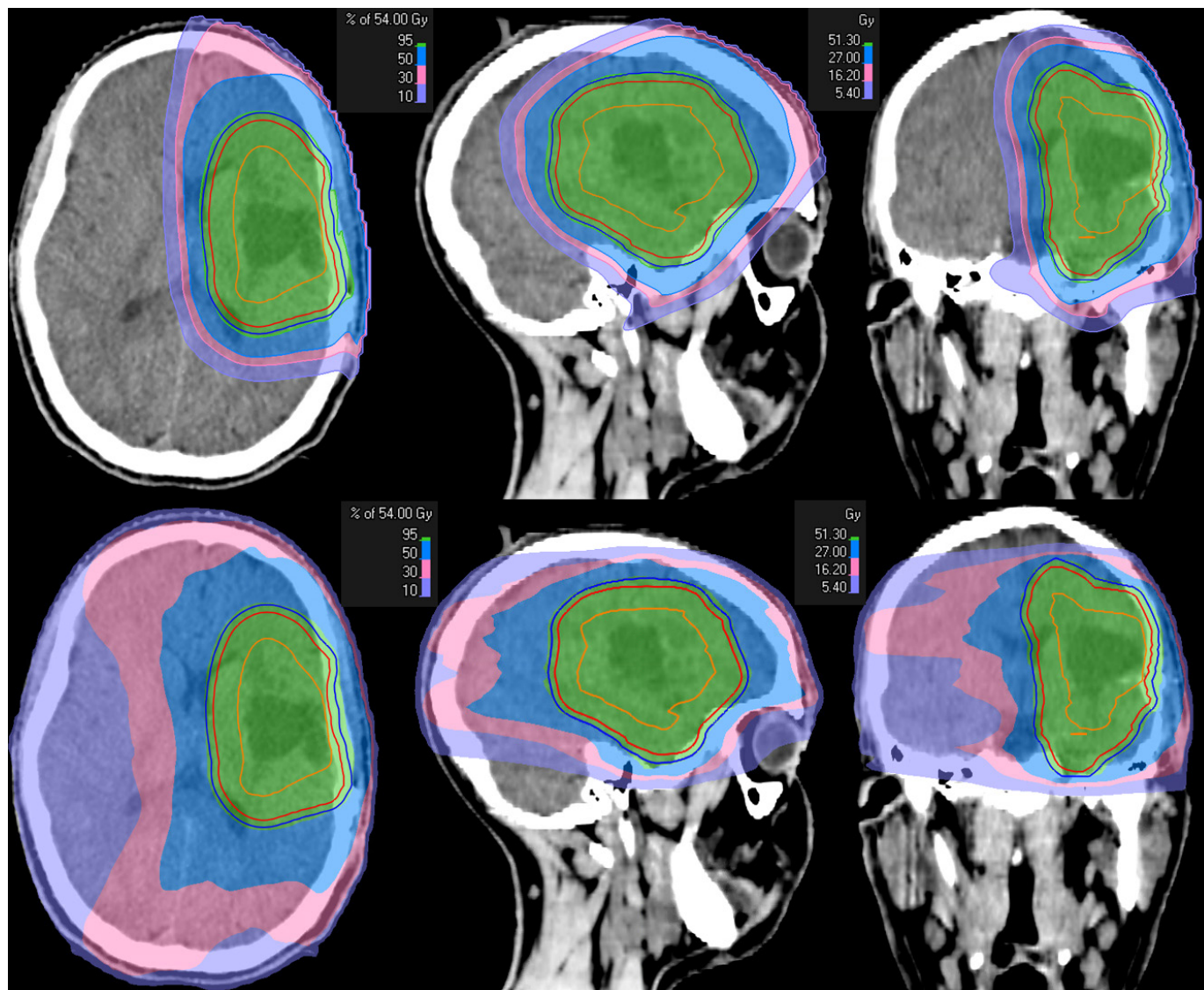


Figure 2 Radiation dose distribution comparing a proton (top) and a photon (bottom) radiotherapy plan for a patient with a diffuse glioma. Radiotherapy delivered with protons is more conformal, sparing brain tissue including organs at risk surrounding the radiotherapy target volume, than treatment delivered with photons. Whether the obvious dosimetric superiority of protons is clinically relevant, especially in patients with diffuse grade 2 and 3 gliomas, is still a matter of debate.

Key secondary outcomes

Two key secondary endpoints will be evaluated at 2 years (table 3): change from baseline in (1) total fatigue score measured by Chalder Fatigue Questionnaire³¹ and (2) composite cognitive score defined as mean z-score of five measures from the cognitive screening tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Secondary and exploratory outcomes

For a full list of secondary outcomes, see table 3. Some secondary and exploratory objectives are detailed below.

Survival parameters

Additional survival parameters including OS, PFS and FIFS at other time points will be analysed. OS is defined as the number of months from date of start of radiotherapy to date of death. PFS is defined as the number of

months from date of start of radiotherapy to the date of first RANO-defined progression³² or death.

Patient-reported outcome measures

Standardised questionnaires will be assessed at different time points to evaluate self-reported domains such as fatigue, anxiety, depression, brain tumour-specific symptoms, health literacy, personality and more (see table 3). In the next protocol version, some PROMs, including fatigue at other time points, will be defined as secondary endpoints. Most PROM parameters are defined as exploratory.

Cognitive functioning

Participants will be screened for cognitive impairment by a CANTAB screening. Additionally, all Norwegian and some Swedish patients will undergo a standard neuropsychological assessment at the same time points. As a full

Table 2 Interventions

	Photons	Protons	Duration	Start	Treatment compensation
Grade 2	(50.4)–54.0 Gy in 1.8 Gy fractions	(50.4)–54.0 Gy RBE in 1.8 Gy RBE fractions	5 fractions per week for 5.5–6.0 weeks, maximum allowed duration 50 days	<60 days following randomisation	Two fractions in 1 day (minimum 8-hour interval) are allowed, but there will be no more than 6 fractions per week
Grade 3	59.4 Gy in 1.8 Gy fractions	59.4 Gy RBE in 1.8 Gy RBE fractions	5 fractions per week for 6.5 weeks, maximum allowed duration 55 days		
GTV	GTV includes surgical cavity and hyperintense tumour suspect lesions on T2/FLAIR sequences according to postoperative and/or dose-planning MRI				
CTV	Grade 2: CTV is GTV+10–(15) mm isotropic expansion Grade 3: CTV is GTV+15–(20) mm isotropic expansion CTV should be adjusted to natural anatomical barriers such as bone, ventricles, falx and tentorium (unless suspected tumour invasion)				
PTV	2–4 mm isotropic expansion, according to institutional practice				
Planning*	The 95% isodose should preferably cover PTV†	Robust evaluation‡			

*Normalisation should preferably be done to the median of CTV, alternatively should the median dose to CTV be kept within the range of 98%–102% of the target dose.
 †Alternatively, more than 98% of PTV should be covered by 95% of the prescribed dose.
 ‡The 95% isodose should cover CTV for all the scenarios (± 3 mm $\pm 3.5\%$).
 CTV, clinical target volume; GTV, gross tumour volume; Gy, gray; PTV, planning target volume; RBE, relative biological effectiveness; T2/FLAIR, T2-weighted fluid-attenuated inversion recovery.

neuropsychological assessment is resource-intensive and time-consuming, an exploratory aim of the PRO-GLIO trial is to evaluate whether cognitive impairment, as identified by a defined CANTAB screening, is comparable with traditional neuropsychological testing. These exploratory analyses will be based on patients in the Norwegian sample and, because of limited resources, only a minority of the Swedish patients. Well-established tests with satisfactory psychometric properties will be applied (see online supplemental table 4). The following functional domains will be evaluated as part of the neuropsychological assessment: manual dexterity, processing speed, mental efficiency, attention, learning and memory, executive functioning, visuospatial functions and language functions. A Global Cognitive Impairment Index will be calculated by dividing the number of impaired domains (at least one test less than 1 standard deviation below mean) by the total number of domains.³³

Progression status

The advantage of protons compared with photons, that is, a more precise dose deposition to the radiotherapy target volume, might be a disadvantage for diffuse gliomas because of their infiltrative nature. Therefore, the rate of local, distant and combined recurrences is of great interest. Local relapse is defined as RANO-defined progression in the radiotherapy target volume (inside the 95% isodose volume). Distant relapse is defined as

RANO-defined progression outside the radiotherapy target volume (outside the 95% isodose volume). MRI will be used to assess neoplastic disease status.

Clinician-rated measures

Change in neurological function will be assessed using the Neurological Assessment in Neuro-Oncology (NANO) scale.³⁴ As epileptic seizures are a frequent and troublesome symptom for patients with diffuse lower-grade gliomas, the change in epileptic seizure frequency and severity will be recorded for each patient. Adverse event (AE) and serious AE (SAE) reporting will be done the first year after start of radiotherapy. Frequency and severity of AEs will be evaluated by Common Terminology Criteria for Adverse Events V.4.0. All symptoms will be registered at baseline and only increased or new symptoms will be recorded as AEs. AEs occurring ≤ 3 months after end of radiotherapy will be regarded as acute, whereas AEs reported > 3 months after end of radiotherapy will be regarded as late AEs. The highest grade for each AE since last study visit or the last 6 months before each assessment will be recorded. A predefined list of adverse events of special interest (AESI) has been established to indicate late side effects of particular interest; these will be assessed during the entire PRO-GLIO Study (see online supplemental table 5).

**Table 3** Outcomes in PRO-GLIO

Parameter/domain	Measure	Time point
Primary endpoint		2 years
Survival	FIFS	
Key secondary endpoints		2 years
Fatigue	Chalder Fatigue Questionnaire, ³¹ total score	
Cognitive impairment	CANTAB, composite z-score of 5 measures of CANTAB score	
Further secondary and exploratory endpoints		
PROMs		5 months, 1, 2, 5, 10 and 15 years
HRQoL	EORTC QLQ-30, ³⁹ EQ-5D-5L (health economy ⁴⁰)	
Brain tumour-specific symptoms	EORTC QLQ-BN20 ⁴¹	
Fatigue	Chalder Fatigue Questionnaire ³¹	
Mental health (anxiety, depressive symptoms)	GAD-7, ⁴² PHQ-9 ⁴³	
Health literacy	HLS-Q12 ⁴⁴	
Personality	Questions similar to the HUNT-3 survey, ⁴⁵ based on Eysenck's Personality Inventory ⁴⁶	
Sleep and lifestyle, sexuality	Questions similar to the HUNT-4 survey ⁴⁷	
Need for rehabilitation	Questions similar to a former trial at OUH ⁴⁸	
Cognitive screening test (CANTAB)		5 months, 2, 5, 10, 15 years
Visual attention	Rapid Visual Information Processing (A Prime), Spatial Span Forward (Span length)	
Visual learning/memory	Pattern Recognition Memory (% correct immediately, % correct delayed)	
Planning/working memory	One Touch Stockings of Cambridge (number solved correctly)	
Clinician-rated measures		
Survival	FIFS, median FIFS	5, 10, 15 years
Neurological function	NANO score ³⁴	2, 5, 10, 15 years
General condition	WHO-ECOG status, KPS score	5 months, 2, 5, 10, 15 years
Epilepsy control	Rate of epileptic seizures	5 months, 2, 5, 10, 15 years
Adverse events	AE, SAE and AESI	End of radiotherapy, 3, 5 months, 1, 2, 5, 10, 15 years
Cognitive impairment	Traditional neuropsychological testing*	5 months, 2, 5, 10, 15 years
Objective		
Survival	OS, PFS, median PFS, median OS	2, 5, 10, 15 years
Pattern of progression/recurrence (local, distant or combined)	RANO ³²	2, 5, 10, 15 years
Concomitant medication	Corticosteroid and AED dose	5 months, 2, 5, 10, 15 years
Basal endocrinological status	Blood tests	Yearly
Health economics		2, 5, 10, 15 years
Incremental cost-effectiveness ratio	Difference in mean cost between groups divided by differences in mean QALYs	
Cost related to loss of production caused by disease and treatment	Healthcare costs: treatment, follow-up and transportation Societal costs: production loss for patients and caregivers	
Lifetime cost/benefit for patients	QALYs	

*Norwegian and some Swedish patients only.

AE, adverse event; AED, anti-epileptic drug; AESI, adverse event of special interest; CANTAB, Cambridge Neuropsychological Test Automated Battery; EORTC QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-BN20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Brain Neoplasm; EQ-5D-5L, EuroQoL-5 Dimensions-5 level; FIFS, first intervention-free survival; GAD-7, Generalized Anxiety Disorder Assessment; HLS-Q12, European Health Literacy Survey Questionnaire, short version; HRQoL, health-related quality of life; HUNT, Health Survey North Trøndelag county; KPS, Karnofsky Performance Status; NANO, Neurological Assessment in Neuro-Oncology; OS, overall survival; OUH, Oslo University Hospital; PFS, progression-free survival; PHQ-9, Patient Health Questionnaire; PRO-GLIO, PROton versus photon therapy in *IDH*-mutated diffuse grade 2 and 3 GLIOMas; PROMs, patient-reported outcome measures; QALYs, quality-adjusted life years; RANO, Response Assessment in Neuro-Oncology; SAE, serious adverse event; WHO-ECOG, World Health Organisation- Eastern Cooperative Oncology Group.

Health economy

A cost-utility analysis will be performed exploring cost per quality-adjusted life years (QALYs) saved of proton therapy in comparison with photon radiotherapy. In each arm, OS data will be weighted with the patients' utility of health. Utility of health is measured by the PROM EuroQol-5 dimensions-5 level (EQ-5D-5L³⁵), and how members of the general population value time with these descriptions of health relative to time without health problems (general population tariff). Different parametric statistical survival models will be fitted to the OS data to extrapolate survival until statistical life expectancy is reached for each patient. Costs in cost-utility analyses are typically differentiated by healthcare costs and societal costs. Healthcare costs include direct medical treatment costs, costs of follow-up and transportation. Societal costs include production loss to the patients and caregivers from disease, disability or treatment. An incremental cost-effectiveness ratio (ICER) will be calculated (see table 3). The calculated ICER will be compared with the absolute prognosis loss (APL) experienced by the patient group (the current loss of health relative to an age-matched general population). In Norway, the APL suggests the monetary level of willingness to pay per QALY for the healthcare provider. Comparing the ICER with the APL will as such allow for assessing the likelihood of cost-effectiveness in a Scandinavian healthcare setting.

Substudies

To evaluate the impact of patients' disease on caregivers, next of kin will respond to four different validated questionnaires, which will all be administered at the same time points as patient PROMs: EQ-5D-5L, the Medical Outcome Survey Short Form-36,³⁶ Caregiver Burden Scale³⁷ and Resource Utilization in Dementia.³⁸

A longitudinal qualitative substudy will be conducted to gain in-depth knowledge about patients' QoL, general well-being, complaints during treatment, and perceived support during diagnosis, treatment and follow-up. These factors will be explored and compared between the two study arms, with 10 Norwegian patients included into each arm (total n=20). Additionally, we will conduct a longitudinal analysis of how each patient's perspective and experiences change over time based on interviews conducted at four time points (baseline, 5 months, 2 years and 5 years). Another longitudinal qualitative substudy is planned in Sweden, where patients, next of kin and bereaved will be interviewed.

Exploratory objectives

In addition to the predefined objectives, the extensive data collection in this trial promises future exploratory objectives related to, for example, reoperations, radiotherapy, radiology, tumour biology, PROMs and cognition. Dosimetry studies including the evaluation of normal tissue sparing and normal tissue complication studies comparing proton and photon therapy will be of particular interest.

Data collection

Data will be collected at each study visit, including PROMs and CANTAB, and all data will be entered into the eCRF Viedoc. Viedoc complies with all relevant health regulations including the general data protection regulation and the Norwegian and Swedish law regulations.²⁹

Study personnel at each site will schedule study visits and provide reminders to participants. SAEs and recurrences in the two treatment arms will regularly be evaluated at Study Steering Committee meetings as part of a continuous risk/benefit assessment.

Sample size

If there is truly no difference between proton and photon radiotherapy on the probability of FIFS after 2 years, then 224 randomised patients (112 in each treatment group) are required to be 80% certain that the upper limit of a two-sided 95% confidence interval (CI) will exclude a difference in favour of the photon radiotherapy of more than 15%. This assumes a 0.8 probability of FIFS in the control arm and no drop-outs. The latter is optimistic; however, given the public healthcare systems in Scandinavia and the severity of the diffuse grade 2 and 3 glioma diagnosis, it is also realistic. An inclusion rate of 75 patients per year, 50 from Sweden and 25 from Norway, will result in 224 included patients in 3 years. Based on Norwegian population-based data, one-third of eligible Swedish and Norwegian patients need to be included for this to happen. Recruitment will continue until the target sample size is reached. The number of included patients in 2022 was 25% higher than expected.

Statistical methods

For sample size and assumptions, see above.

Statistical analysis plan

Further details and specifications will be given in a separate statistical analysis plan (SAP). This SAP will be prepared and finalised prior to locking of the database and before any efficacy analyses. The SAP will be the leading document for the statistical analyses. Any discrepancies between the protocol and the SAP will be discussed when interpreting the results.

Populations of analysis

The following populations will be considered for the analyses:

- ▶ Per-protocol set (PPS): the primary analysis will be performed in the PPS because this is a non-inferiority trial. The PPS is defined as all randomised participants having completed the assigned radiotherapy according to protocol.
- ▶ Full analysis set (FAS): the FAS is defined as all randomised participants regardless of protocol adherence (intention-to-treat approach).
- ▶ Safety set: the safety set will be the same as the PPS.

Primary endpoint

FIFS at 2 years will be evaluated in a non-inferiority test in the PPS. The primary analysis of the primary endpoint will be calculated by adjusted Kaplan-Meier curves. These will be adjusted for the stratification factors (grade, histology and study site) and important predictive variables (age, target volume size, target volume localisation and neoplastic situation/primary diagnosis or recurrence). The difference in the probability of FIFS at 2 years will be extracted by the Kaplan-Meier estimator and a two-sided 95% CI of the difference will be calculated by bootstrapping. The upper limit of this 95% CI will be compared against a non-inferiority margin of 15%.

The primary null hypothesis is that at 2 years, there is a difference in the probability of FIFS of at least 15% in favour of the photon therapy. The null hypothesis is rejected if the upper limit of the 95% CI of the absolute difference in FIFS probability at 2 years does not include 0.15. Secondary analyses of the primary endpoint include the above-described analysis in the FAS as well as estimation of the difference in the probability of FIFS at 2 years using a Cox proportional hazards model (only if the proportionality assumption is fulfilled) in the PPS and FAS. We will further calculate the restricted mean time to FIFS in both arms.

Key secondary endpoints

The two key secondary endpoints (change in fatigue total score and change in composite CANTAB score) will be evaluated in a superiority test in the FAS. The primary analysis of the key secondary endpoints will be based on a linear mixed-effects model with random intercept and random slope, treatment–time interaction and adjusted for the stratification variables (grade, histology and study site) and baseline value as fixed effects. The effect estimates will be the difference in the adjusted marginal mean score extracted from the model at 2 years with two-sided 95% CIs. The null hypothesis for the key secondary endpoints is that there is no difference in change from start of radiotherapy of the adjusted marginal mean scores of (1) total fatigue and (2) composite CANTAB score at 2 years comparing proton with photon radiotherapy. The null hypotheses (no difference) will be rejected if the p-value is below the significance level of 0.05.

Other secondary endpoints

Secondary survival endpoints will be analysed using the same methods as the primary outcome in the PPS and FAS. Repeated continuous and binary secondary endpoints will be analysed as for the key secondary endpoints in the FAS and PPS. All efficacy analyses will be presented with estimated differences and 95% confidence limits of the treatment effect; a p-value will be provided for the superiority endpoints. Further exploratory analyses will be specified in the SAP.

Health economy endpoints

Estimates on ICER of proton therapy over photon radiotherapy will include costs and health outcomes

summarised in QALYs from an extended health service perspective. An analysis that incorporates patients' loss of production when unable to work will be performed, as well as an analysis considering the impact of the caregiver burden on the health of next of kin.

Statistical methods to handle missing data

For the primary outcome, participants who are lost to follow-up will be censored at the date of last known alive and without need of antineoplastic therapy not part of primary treatment. For outcomes measured repeatedly, missing values during follow-up will be handled implicitly by the mixed model. Imputation of missing baseline values will be specified in the SAP. If missing data are regarded as having a significant effect on the conclusions of the trial, sensitivity analyses with different methods for handling missing data will be included and specified in the SAP. Such methods may include complete case analyses, last observation carried forward, worst case/best case imputation and multiple imputation techniques.

Oversight and monitoring

The Study Steering Committee is composed of health-care professionals from Norway and Sweden and a patient representative; they will have regular, at minimum yearly, meetings. Meetings with representatives from all participating centres (study group) will be held when necessary. In the time between study group meetings, the members of the Study Steering Committee shall act as contact persons and will have an executive role.

PRO-GLIO will be monitored to ensure optimal data quality and consistency. Monitoring will be performed by Research Support Services at OUH with assistance from Gothenburg. Monitoring for Norwegian sites will be performed by the Clinical Trial Unit (CTU) at OUH or by locally based monitors under the supervision of the CTU at OUH. A monitor from Gothenburg will monitor all Swedish study sites. To coordinate and assure consistent monitoring across all centres, the CTU at OUH will take a lead monitoring function for all sites.

Ethics and dissemination

PRO-GLIO will adhere to the ethical recommendations of the Helsinki Declaration, the International Committee of Harmonisation-Good Clinical Practice guidelines and Norwegian and Swedish laws and regulations. This includes signed written informed consent from all participants, voluntary participation and the option to withdraw from the study at any time. PRO-GLIO has been approved by independent ethical committees in Norway (Regional Committee for Medical & Health Research Ethics, South East Norway, Section C: reference number: 265626) and Sweden (The Swedish Ethical Review Authority, Västra Götaland: reference number: Dnr 2021-04239 and Dnr 2022-01305-02) before trial start. Protocol amendments to improve study execution and quality will be continuously evaluated and initiated by the Study Steering Committee. Decisions to publish PRO-GLIO results will

be made by the study group and all presentations of data from PRO-GLIO will be made only after agreement within this group. Study outcomes will be circulated to all participating centres and will be published in peer-reviewed scientific journals and presented at relevant national and international conferences and expert forums. Full protocol and statistical codes are available upon request.

Trial status

This manuscript is based on protocol version 3.0, dated 14 February 2022, which is active in Norway, and protocol version 3.1 dated 4 March 2022, which is active in Sweden. Recruitment started January 2022 in Norway and May 2022 in Sweden. Trial recruitment started in 2022 for four sites, while the rest will start inclusion in 2023. The analysis of the primary endpoint is estimated in 2028, while final data collection is expected in 2041. The trial was prospectively registered in ClinicalTrials.gov (NCT05190172).

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Contributors PBrandal, MB and KW conceived the idea for this study. PBrandal is the principal investigator and the coordinating investigator in Norway, while MB is the coordinating investigator in Sweden. PBrandal, KW, MB, HR, CG, CK, THN, LCH, IMHB, MG, HL, LA, CM, ASJ, C-JB, CR and ICO contributed to writing of the study protocol. TPH, MEE, MG, CR, JM, KA, IRaunert, TH, MH, MS, HM and IK have all contributed to the dummy run procedure. PBrandal, KW, MB, LCH, MS, HM, HB, DG, JB, T-CAJ, TSS, KM, ØH, Pbergström, MA, LD, MG, HG, ASJ and EO-V-M are responsible for patient recruitment in this trial. RJL and ED are user representatives in this trial. CSR is the study statistician and will write the statistical analysis plan and perform the statistical analysis together with ICO. IMHB and Iryden will conduct neuropsychological testing. LCH is a doctoral fellow, while IMHB is a postdoctoral fellow in this trial. All authors helped draft the manuscript and consented to publication. All authors read and approved the final version of the manuscript.

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