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Proton versus photon radiotherapy in adults with primary brain tumors evaluating functional survival: a phase 3 randomized controlled trial study protocol (PRIDE)

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Abstract

Background Radiation therapy (RT) plays a significant role in the multimodal management of primary brain tumors, improving oncological outcomes. However, despite advances such as Intensity-Modulated Radiation Therapy (IMRT), photon-based RT inevitably exposes normal organs to low-dose radiation, leading to long-term functional morbidities like cognitive decline, endocrine dysfunction, auditory toxicity. These late effects are particularly concerning in patients with favorable prognoses and protracted survival. Proton beam therapy (PBT), owing to its unique physical properties, holds promise for better functional preservation, but robust clinical data in adults are lacking.

Methods The PRIDE study is a prospective, open-label, phase 3 randomized controlled trial enrolling adults aged 18–70 years undergoing focal cranial RT with conventional fractionation for primary brain tumors with expected survival > 5 years at Tata Memorial Centre, Mumbai. Participants will be randomized 1:1 to receive either photon-IMRT (standard arm) or PBT (experimental arm), stratified by age, tumor type, proximity to the hypothalamic-pituitary axis, and radiation dose. The primary endpoint is 5-year functional survival, defined as survival without functional deterioration (neurocognitive decline, significant ototoxicity, new or worsening endocrine dysfunction, neurological impairment, severe radio-necrosis, disease progression, or death). Secondary endpoints include patient-reported quality of life and health economic analysis. Survival outcomes will be analyzed using Kaplan-Meier methods with log-rank test. Neurocognitive and quality-of-life data will be evaluated using linear mixed-effects and non-parametric tests. A total of 156 patients will be enrolled, accounting for 20% attrition, to detect a 25% absolute improvement in 5-year functional survival favoring PBT (65% vs 40%, HR 0.47, α=0.05, power=80%). An interim analysis has been planned using the O'Brien-Fleming rule after 50% of the events (n=28).

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Discussion This trial will provide level 1 evidence investigating the role of PBT in functional outcomes among adults with primary brain tumors. If study endpoint is achieved, PBT will be considered as standard of care guiding contemporary neuro-oncology practice.

Registration The trial has been approved by the Institutional Ethics Committee of Tata Memorial Centre, Mumbai. The trial has been registered with the Clinical Trial Registry of India (CTRI/2025/03/082568) and Clinicaltrials.gov (study identifier NCT06831461).

Keywords Proton beam therapy, Brain tumours, Neurocognition, Functional survival, Randomized controlled trial

Introduction

Primary brain tumors account for approximately 2% of all malignancies, with 80% of these occurring in adults [1]. Radiation therapy (RT) plays a critical role in the multimodality management of primary brain tumors, contributing to improved local control and prolonged progression-free survival across a broad range of tumor types, making it an integral part of multimodal management [2]. However, despite advancements like Intensity-Modulated Radiation Therapy (IMRT), modern photon radiation is associated with unavoidable low-dose exposure to normal brain tissues. This can lead to several late side effects that impact the functionality of adult patients with brain tumors, such as cognitive impairment, endocrine dysfunction, and auditory impairment [3, 4]. Although some of the radiation-related side effects are often reversible with rehabilitation, they still contribute to economic toxicity and almost universally lead to a deterioration in overall quality of life (QoL).

As the magnitude of late functional effects is dose-dependent, recent advancements in radiation therapy have aimed to increase precision, thereby minimizing damage to surrounding healthy tissues [5]. The efforts to reduce treatment-induced morbidities are of particular interest in patients diagnosed with tumors with good prognosis and, therefore, higher probability of survivorship [6]. Particle beam therapy, such as proton beam therapy (PBT), with its unique physical properties, including a finite range and sharp distal dose fall-off known as the Bragg peak, allows superior dose conformality and reduced total integral dose to organs at risk (OAR). The dose distribution comparing photon and proton therapy has been shown in a patient with right temporal isocitrate dehydrogenase (IDH) mutant glioma (Fig. 1). The corresponding dose-volume parameters demonstrating lower doses received by relevant organs at risk (eye, cochlea, hippocampus) are presented in Fig. 2. The increasing availability of PBT facilities offers an option for further reducing RT-induced late effects.

While there is substantial dosimetric evidence supporting the benefits of PBT compared to photon therapy, clinical efficacy in functional preservation has been demonstrated primarily in pediatric populations [7, 8], particularly in the context of whole craniospinal irradiation (CSI). Studies have shown favorable neurocognitive and academic outcomes with PBT compared to photon therapy in children [9]. In adults, the evidence is limited to dosimetric studies, and the extent of its clinical benefit remains uncertain. Existing clinical and dose-modeling reports often used older passive scattering techniques, while newer technologies, such as pencil beam scanning, offer greater potential for functional sparing [10]. Overall, there is currently no high-quality, randomized data comparing the outcomes of proton versus photon therapy in adults with primary brain tumors. To address this knowledge gap, the current randomized controlled trial compares PBT with standard photon therapy, focusing on cognitive and functional preservation in adults undergoing focal cranial irradiation.

Study methodology

Study design/ population

This is an open-label, prospective, superiority, 2-arm, phase 3 randomized controlled trial. Patients will be screened from the neuro-radiation oncology clinic at Tata Memorial Centre, Mumbai. Patients aged 18 to 70 years who are planned for focal cranial radiotherapy for primary central nervous system (CNS) tumors meeting eligibility criteria will be considered for the study. Indications for radiation will be as per standard institutional practice, primarily decided by histology, tumor grade, molecular features (as appropriate for selected histologies), type of tumor resection, and extent of disease. Patients with an expected life expectancy of more than 5 years, as per published literature and institutional data, will be considered eligible for the study. This will include but is not limited to the diagnosis of low-grade glial/ glioneural tumors, IDH-mutant grade 2/3 gliomas (astrocytoma and oligodendroglioma), ependymoma, meningioma, pituitary tumor, craniopharyngioma, schwannoma. In some instances, which are treated based on a radiological diagnosis (without needing a histopathological diagnosis), like schwannoma, meningioma, will be eligible for the study. The trial (protocol version 1.0) has been approved by the Institutional Ethics Committee of Tata Memorial Centre, Mumbai. The trial has been registered with the Clinical Trial Registry of India (CTRI/2025/03/082568, dated 18.03.2025) and

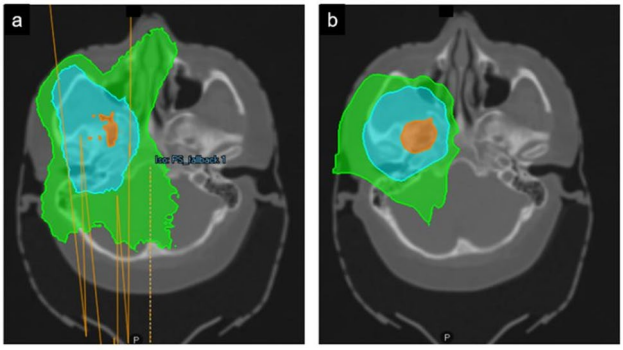

Fig. 1 Dose distribution comparing photon radiation using VMAT (**A**) and proton beam therapy (**B**) for a patient with right temporal IDH mutant grade 2 astrocytoma. The orange, cyanide, and green regions denote the 95%, 50%, and 25% dose regions, demonstrating proton beam therapy associated with a lower dose spillage to the surrounding region (right cochlea, right eye, brainstem)

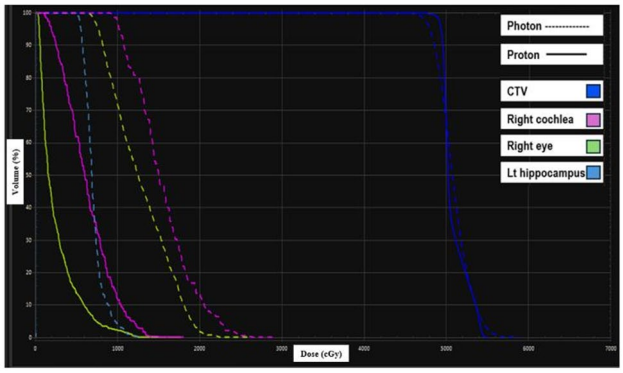

Fig. 2 The dose-volume parameters for the above patient for the clinical target volume (demonstrating better coverage), right cochlea, right eye, and left hippocampus. Kindly note that proton beam therapy delivered no dose to the left hippocampus

Clinicaltrials.gov (study identifier NCT06831461, dated 18.02.2025).

Inclusion criteria

1. Primary brain tumors
2. Age at irradiation: 18 to 70 years
3. Karnofsky Performance Status ≥ 60
4. Diagnosis (histopathological/ radiological) of primary brain tumor with an expected survival of > 5 years (e.g., grade 2–3 diffuse glioma, low-grade glial/ glioneuronal tumors, ependymoma, meningioma, pituitary tumors, schwannoma, craniopharyngioma, etc.)
5. Planned for focal cranial radiotherapy
6. Informed consent taken

Exclusion criteria

1. Re-irradiation
2. Palliative radiotherapy
3. Multifocal or multicentric disease
4. Planned for whole brain irradiation or craniospinal irradiation
5. Planned for hypo-fractionated or stereotactic radiotherapy

Study intervention

After meeting study eligibility and discussion with patients and caregivers by the study investigators, consent forms will be served and accrued in the study once a signed consent form is obtained. Patients considered for fractionated radiotherapy following maximal safe resection with histopathological confirmation and expected survival of more than 5 years will be screened for the study. Patients who are not suitable for surgery or biopsy and considered to be treated based on radiological diagnosis, like vestibular schwannoma, cavernous hemangioma, or other skull base tumors, will also be eligible for the study following discussion in the multidisciplinary tumor board. Participants will be randomized in one of the two arms (standard arm or experimental arm) in a 1:1 ratio via computerized software using a permuted block design, accounting for the following stratification factors:

1. Diagnosis of tumor type on histopathology/radiology (diffuse glioma vs. others)
2. Age during radiation (18–39 vs. ≥ 40 years)
3. Proximity to the hypothalamic-pituitary axis (tumor within 1 cm vs. > 1 cm of hypothalamic-pituitary axis)
4. Radiation dose (≤ 54 Gy vs. > 54 Gy)

Treatments

Patients in the standard arm will undergo focal cranial radiotherapy using photons (X-rays) with image guidance using IMRT, volumetric modulated arc therapy (VMAT), or helical intensity-modulated techniques. The patients in the experimental arm will undergo focal radiotherapy to an equivalent dose using protons (Cobalt Gray Equivalent) with pencil beam scanning or volumetric modulated proton arc therapy. The radiation dose and volumes will be guided by tumor type and molecular features without any influence from the current study on radiation protocols. Baseline workup investigations for diagnosis and treatment plan will be undertaken per standard practice, including histopathological evaluation, molecular evaluation, blood analysis, and imaging with magnetic resonance imaging (MRI) brain tumor protocol. Patients will be simulated in a supine position and immobilized using head-neck thermoplastic masks fitted to a Universal Base Plate according to the institutional protocol. Radiation planning non-contrast computed tomography (NCCT)

scan will be acquired from the top of the vertex to the clavicle with a slice thickness of 1.25–2.5 mm. Planning MRI of the brain will be done per institutional practice, including 3D sequences of T1-contrast, 3D T2-weighted propellor, 3D T2-FLAIR sequences, and additional sequences like FIESTA or CISS as indicated (for skull base targets) is needed within 4 weeks from starting radiation. In our standard institutional practice, the planning CT and MRI are scheduled on the same day or maximum within an interval of 24–48 h, and treatment is started in 5–10 days, allowing time for contouring, planning, and quality assurance. Planning PET scans will be done in patients with tumor diagnoses of meningioma, schwannoma, and pituitary tumors as clinically indicated.

The contouring of target volumes will be done by the radiation oncologists using registrations of appropriate planning imaging to delineate gross tumor volume (GTV), clinical target volume (CTV), and planning target volumes (PTV) as applicable for the tumor type without any influence of the study arm. Organs at risk (OAR) like the hippocampus, temporal lobes, amygdala, brainstem, optic nerves and optic chiasm, pituitary gland, cochlea, oral cavity, eye, lens, etc., will be contoured for the plan as per institutional practice. Dose prescriptions will be done as per standard practice. Typically, the target volume dose prescriptions currently for the common histologies likely to be included in the study are as follows: diffuse gliomas (55.8–59.4 Gy using 1.8 Gy per fraction depending upon subtype i.e., oligodendroglioma vs. astrocytoma); ependymoma (59.4 Gy using 1.8 Gy per fraction), meningioma (54 Gy to 60 Gy using 1.8/2 Gy per fraction depending upon grade, location, molecular features); craniopharyngioma, schwannoma (54 Gy in 30 fractions); circumscribed glioma, low-grade glioma (50 Gy to 54 Gy in 1.67/ 1.8 Gy depending upon location); pituitary tumors (45 Gy in 25 fractions). To avoid any potential bias from the study arm, the dose fractionation needs to be defined before randomization, which also serves as a stratification factor. The OAR tolerance will be used as per standard practice and existing literature. The radiation plan will be made in the Treatment Planning System (TPS) by designated medical physicists and reviewed by the responsible radiation oncologist. Given the diverse location of the target volumes for patients accrued in the study, no predefined dose-volume constraints are mandated. However, the principle of low as reasonably achievable (ALARA) will be followed by practicing reasonable dose-volume constraints as per current literature and institutional practice. As a part of quality assurance, the radiation target volume and plan will be individually reviewed in the radiation-planning review meeting, comprising radiation oncologists, medical physicists, neuroradiologists, and radiation therapy technologists. Treatment will be delivered on photon or proton facilities equipped with image guidance platforms. All patients will be reviewed on a weekly basis by radiation oncologists to monitor for acute radiation-related toxicities using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 scales. All toxicities occurring within 60 days from the completion of radiotherapy and directly ascribed from the radiation treatment will be labeled as acute radiation effects. Interval imaging and adaptive planning will be done as per standard practice in both study arms without any influence from the study participation. Chemotherapy (concurrent or adjuvant) will be given as indicated (IDH-mutant glioma).

Follow-up

After completion of radiotherapy, patients will undergo scheduled regular clinical and radiological follow-ups as per standard practice without any influence from the study. The first imaging after radiation for IDH-mutant gliomas is done 1-month post-radiotherapy, before starting adjuvant chemotherapy, and after that during adjuvant chemotherapy and at the conclusion. Otherwise, for high-grade tumors (not planned for adjuvant chemotherapy) treated with radiation, the first imaging is done 1–2 months, while for low-grade and benign tumors, it is done 2–3 months after completion of radiotherapy. As per standard practice, after completing all scheduled treatments (including chemotherapy), patients will undergo scheduled clinical evaluation every 3–6 months for the initial 2 years and every 6 months after that. Institutional protocols include surveillance imaging every 6–12 months or as per clinical indication (during new symptoms), which will apply to the current study. Any disease recurrence or complications arising from treatments will be treated per standard practice and discussed in the multidisciplinary joint neuro-oncology clinic as required.

Functional assessments

Neurocognitive evaluation using age-appropriate tests by psychologists will include the Wechsler Adult Intelligence Scale test, which provides the Full-Scale Intelligence Quotient (FSIQ) and other subdomains as the Verbal Quotient (VQ), Performance Quotient (PQ). Neurocognitive assessment will be done before starting radiotherapy (baseline), post-radiotherapy 6 months, 1 year, and annually after that.

To evaluate the endocrine function, the pituitary profile will be tested, which includes thyroid-stimulating hormone, free T4, T3, insulin-like growth factor (IGF)-1, growth hormone (GH), estrogen, testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), cortisol, and prolactin levels. The auditory function will be tested using pure tone audiometry. Endocrinal and auditory

assessments will be done before starting radiation and annually after that.

Patient-reported outcomes will be recorded using the European Organisation For Research and Treatment of Cancer (EORTC) QLQ core (C-30) and brain (BN-20) modules for quality-of-life assessment before starting radiation, once during mid-radiotherapy (3rd to 4th week), at conclusion, 1–3 months after completion (during 1st follow-up visit after radiotherapy), 6 months, 1 year after completion, and annually after that. The sleep and dream will be assessed through the Pittsburgh Sleep Quality Index (PSQI) and Mannheim Dream questionnaire (MADRE) questionnaires, respectively. The time points of assessment will be similar to QOL assessments.

All pre-radiation (baseline) investigations are required to be done within 1 month before the start of the radiotherapy. The study workflow has been summarized in Fig. 3.

Oncological and toxicity assessments

The assessment of disease status and radiation-induced toxicity in the form of radio-necrosis will be done by serial clinical and imaging surveillance, as outlined earlier. In equivocal cases of radio-necrosis, additional imaging with amino acid PET will be done and discussed in the multidisciplinary joint neuro-oncology meeting. Disease progression will be defined by the response assessment in neuro-oncology (RANO) 2.0 criteria.

Statistical considerations

The hypothesis of the study is Proton beam therapy (experimental arm) is superior in functional preservation compared to photon therapy (standard arm) in adults with primary brain tumours receiving focal radiotherapy with conventional fractionation.

Outcome measures

The study's primary and secondary outcome measures of interest have been summarized in Table 1. The primary

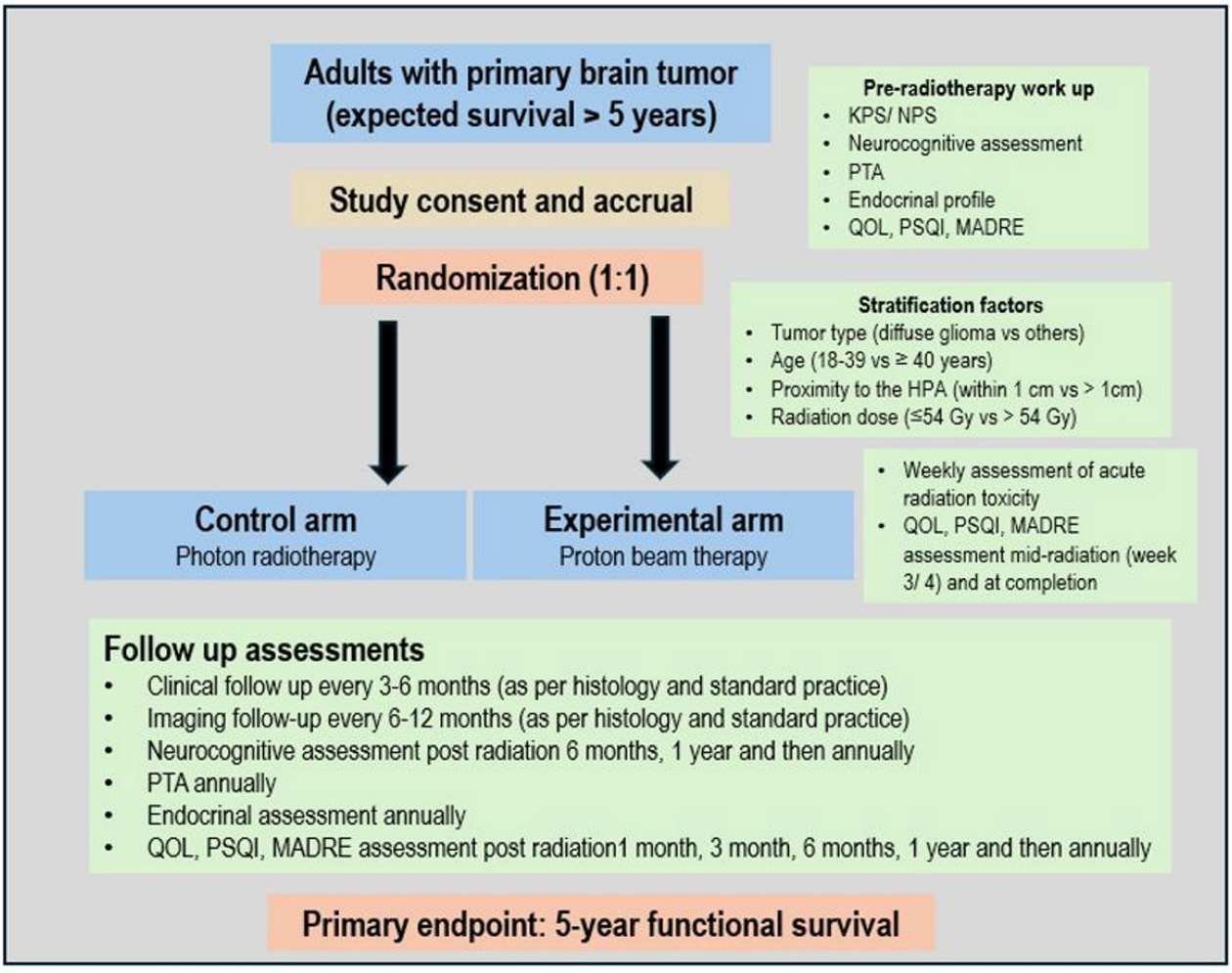

Fig. 3 Schematic workflow of the study showing the scheduled assessments at different time points

Table 1 Objectives and endpoints of the study

Study Objective	**To compare the clinical utility of proton therapy versus photon therapy in preservation of neurological functions in adult patients with brain tumours receiving focal radiotherapy.**
Study Endpoints	
Primary Endpoint	5-year rate of functional survival (overall survival without functional deterioration) defined as the time from randomization to any of the following events:
1. Cognitive decline	A drop of 10% from baseline (pre-radiotherapy) in the FSIQ or any sub-domains of the neurocognition test.
2. CTCAE v.5 gr ≥ 2 ototoxicity	Threshold shift of > 25 dB averaged at 2 or more contiguous test frequencies in at least one ear, or profound bilateral loss (absolute threshold > 80 dB HL at 2 kHz and above, or hearing loss limiting instrumental ADL, or needing a hearing aid or intervention. In patients with pre-existing hearing loss because of tumor location (e.g., acoustic neuroma) or as a comorbidity, a decline of hearing loss by one grade in the CTCAE scale is required to be considered as an event. Also, in some instances where radiation dose to the cochlea is clinically insignificant (e.g., high frontal, parietal location) and future development of hearing loss cannot be related to the radiotherapy (e.g., age-related or other cause assigned after detailed auditory evaluation by a specialist) will be reviewed by study investigators and will be not be defined as an event for the study.
3. Endocrinal dysfunction:	Significant decline in one or multiple pituitary axes and/or starting/increasing doses of hormone supplements.
4. Neurological impairment	A decrease in the NPS by 2 points or KPS by at least 30 points from pre-radiation status will be considered as an event. Fulfilling one of these criteria will be regarded as an event unless temporal causation is directly attributable to other non-neurological causes.
5. CTCAE v.5 gr ≥ 3 radio-necrosis	A disorder characterized by a necrotic process occurring in the brain and/or spinal cord causing severe symptoms; intravenous medical intervention indicated; excluding corticosteroid.
6. Disease progression	In cases of glioma, the progression of the disease will be defined by RANO 2.0 criteria, which integrate MRI changes, clinical findings, and changes in steroid use (54).
7. All-cause mortality	Death from disease progression or any other cause, including toxicity, will be considered as an event.
Secondary Endpoints	1. Overall survival and Progression-free survival. 2. Radiation-induced acute toxicity (during and within 60 days of completion of radiotherapy, using CTCAE v.5). 3. Cumulative incidence of sub-domains of functional survival. 4. Quality of Life (patient-reported outcomes). 5. Post hoc analysis per stratification factors.
Tertiary endpoints	1. Cost-effectiveness analysis. 2. Cost-benefit analysis. 3. Sleep scores using Pittsburg Sleep Quality Index (PSQI). 4. Dream analysis using the Mannheim Dream questionnaire (MADRE).

endpoint of the study is the 5-year rate of overall survival without functional deterioration (functional survival = fS), calculated from the date of randomization. An event concerning the primary endpoint will include (See Table 1 for definitions) Neurocognitive decline, CTCAE grade ≥ 2 ototoxicity, new endocrine axis dysfunction or worsening of pre-existing dysfunction, neurological and functional impairment, CTCAE gr ≥ 3 radio-necrosis, disease progression, and all-cause mortality.

Sample size calculation

The sample size calculation is based on the primary endpoint of functional survival at 5 years. The 5-year functional survival rate is considered to be 40% in photon radiotherapy (standard arm). To demonstrate the superiority of proton beam therapy, the 5-year functional survival needs to be 65% (hazard ratio 0.47, two-sided $\alpha = 0.05$, power = 80%), 65 patients need to be randomized in each arm (35 and 21 events in the standard and experimental arms, respectively). Accounting for a 20% attrition rate, the final sample size will be 156.

Statistical analysis

- **Primary endpoint**: Functional survival will be tested using the Kaplan-Meier method, and differences between the treatment arms will be compared using the log-rank test. The date of randomization will be considered the baseline for survival analysis, and a p-value of 0.048 (two-sided) will be regarded as statistically significant during the final analysis. Patients lost to follow-up will be censored for the assessment of functional survival, while death from any cause will be considered as an event as defined in the functional survival (in either arm).
- **Secondary and tertiary endpoints**: The survival analysis of overall survival (OS) and progression-free survival (PFS) will be tested using the Kaplan-Meier method, and differences between the treatment arms will be compared using the log-rank test. The date of randomization will be considered the baseline, with the date of death considered an event for OS, while the date of radiological progression will be regarded as an event for PFS. Patients who are lost to follow-up will be censored. The slope of FSIQ and

other domains of neurocognition between the two study arms at different time points will be compared using linear mixed-effect regression models. Endocrine and auditory function will be analyzed using the Wilcoxon Rank Sum test for numerical data and the Fisher's Exact test or the chi-square test for categorical data, as applicable. Toxicity will be documented using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and compared between the groups using the Chi-square test or Fisher exact test as appropriate. Summary scores for QLQ-C30 and BN20 will be calculated from raw scores as per the EORTC scoring manual, ranging from 0 to 100, with 0 being the worst and 100 being the best possible score. Shapiro-Wilks normality test will be used to assess the normality of data, with data being considered skewed if $p < 0.05$. For non-normally distributed data, related samples two-way Friedman test, the non-parametric equivalent of repeated measures analysis of variance will be used to analyze differences in paired summary scores at any time point compared to baseline. Cost-effectiveness analysis will be measured using the Markov model. The cost-benefit analysis will be done by accounting for the direct and indirect costs associated with radiation treatment, the cost of toxicity management, and survival outcomes. The sleep and dream scores will be calculated using the PSQI and MADRE questionnaires, with composite and the subdomains computed using the manual. The scores between the two treatment arms and other clinical factors will be compared using Mann Whitney U test and independent t-test as appropriate.

- **Interim analysis**: An interim analysis using the O'Brien-Fleming rule will be planned after 50% of the events ($n = 28$), which is estimated to happen around 4.4 years from the start of accrual. To demonstrate the superiority of proton beam therapy over photon radiotherapy during interim analysis, the p-value is required to be < 0.005, and if the trial continues after the interim analysis, the p-value for the final analysis will be 0.048.

Discussion

Advancements in cancer-directed therapies have consistently improved disease-related outcomes. Patients with certain histologies (e.g., low-grade gliomas, meningiomas, craniopharyngioma, and pituitary tumors) exhibit prolonged survival, with 10-year survival rates ranging from 80 to 100% following multimodality treatment. These improved outcomes have encouraged researchers to focus more on functional preservation, particularly in long-term survivors. Recent progresses in radiation therapy have aimed to increase precision, thereby minimizing damage to surrounding healthy tissues [5]. The routine use of multiparametric imaging like magnetic resonance imaging (MRI) and positron emission tomography (PET) for target volume and organ-at-risk (OAR) delineation, volumetric modulation of radiation beam intensity, inverse planning algorithms with specific dosimetric objectives for targets and OARs, and three-dimensional image guidance during delivery now represent the standard of care in neuro-oncology practice [11, 12]. These refinements have been gradually incorporated into clinical practice, supported by evidence of both dosimetric and clinical benefits [6, 13].

Particle therapy, such as proton beam therapy, has been available for clinical use in Western countries for several decades but is a relatively recent addition to the Indian healthcare system. The depth-dose distribution of a proton beam, characterized by the Bragg peak, offers a key advantage over conventional photon therapy by minimizing radiation exposure to surrounding healthy tissues. The Bragg peak allows reduced radiation exposure to tissues located upstream of the tumor and completely spares tissues downstream of the target. Along with its favorable physical properties, the technological aspects of proton therapy are also evolving [14]. Intensity-modulated proton therapy (IMPT), using spot scanning, allows for dose painting and image guidance during delivery, increasing the accuracy of radiation delivery and potentially reducing the margins required for treatment [15, 16]. Thus, modern proton therapy represents one of the most conformal radiation techniques currently available, offering the most optimal sparing of organs at risk.

The hypothesis that PBT can reduce toxicity is based on the fact that the majority of radiation-induced long-term effects are deterministic, with a finite threshold, and the severity is dose-dependent. Although this hypothesis is primarily based on retrospective dosimetric correlations, the proof of concept comes from clinical investigations that have shown reduced late effects with better sparing of the OARs. However, despite the clear dosimetric advantages, proving that technological advancements translate into significant clinical benefits in terms of efficacy and long-term side effects has often been challenging. The key domains of radiation-induced functional toxicity impacting the QoL of adults with primary brain tumors, particularly in the context of focal irradiation, are discussed below.

Long-term cognitive function in brain tumor survivors is a major concern in clinical practice. Cognitive decline in these patients is multifactorial, influenced by age, tumor location (especially in the temporal and frontal lobes), hydrocephalus, antiepileptic drugs, chemotherapy, and radiation dose to critical neural structures [17–22]. Radiotherapy has been associated with impairments

in processing speed and executive function [23–25], with the reported prevalence of cognitive deficits ranging from 19% to 83% in adult brain tumor patients [19, 26]. The hypothesized mechanism for radiation-induced cognitive impairment involves the progressive depletion of neural stem cells in the hippocampus and dentate gyrus, regions critical for learning and memory [27, 28]. Additionally, radiation-induced brain injury is linked to neuroinflammatory cascades, including disruption of the blood-brain barrier (BBB), decreased hippocampal neurogenesis, and increased astrocytic senescence [29].

Dosimetric studies have consistently shown that higher RT doses to the left temporal lobe, hippocampus, and thalamus correlate with declines in verbal memory, executive function, and processing speed [30–32]. High-precision conformal radiotherapy has been proven to improve neurocognitive outcomes in pediatric patients with low-grade glioma and benign tumors in a prospective randomized trial [6]. Even with proton beam therapy, studies have clinically meaningful differences in cognitive outcomes with sparing the left temporal lobe and hippocampus in childhood brain cancers [33]. However, most prospective data of cognition sparing still come from younger, more vulnerable populations, where preserving critical brain structures is particularly important due to ongoing neurodevelopment and neuroplasticity. In contrast, studies involving adult patients—such as the NOA-07 trial in adult medulloblastoma and other glioma cohorts—suggest that long-term neurocognitive function can remain relatively preserved after radiotherapy [34, 35]. Evidence of proton therapy for preserving neurocognitive functioning in adults is limited to single-arm prospective studies, showing encouraging results [36]. Robust clinical evidence supporting cognitive preservation with proton therapy over IMRT remains lacking. A dosimetric modeling study from the Princess Margaret Cancer Centre estimated only modest improvements in verbal fluency [37]. Despite convincing dosimetric superiority, clinically meaningful cognitive benefits of proton therapy over photon therapy are yet to be firmly established.

Endocrine dysfunction in brain tumor survivors is closely associated with the proximity of the tumor (or radiation target) to the hypothalamic-pituitary axis (HPA). The incidence of endocrine deficiencies increases with time since radiotherapy and the dose delivered to the HPA and decreases with older age at the time of treatment [38]. In tumors such as pituitary adenomas and craniopharyngiomas, endocrine dysfunction requiring long-term hormonal replacement is observed in over 80–90% of patients. However, hypopituitarism is also common in non-pituitary brain tumors, with reported incidences ranging from 41% to 66% in adult patients [39]. The analysis of endocrine outcomes from the current study will provide information related to the role of PBT in preserving endocrine dysfunction.

Auditory dysfunction, particularly sensorineural hearing loss (SNHL), is an understudied late effect of cranial RT in adults. Most available data come from head and neck cancers, particularly nasopharyngeal carcinoma, where outcomes are confounded by concurrent chemotherapy and higher radiation doses, limiting applicability to primary brain tumors. Factors such as younger age at the time of RT and higher cochlear doses (> 30–35 Gy) significantly increase the risk of SNHL in patients with primary CNS tumor [40, 41]. In proton therapy, mean cochlear dose has also been linked to mild hearing loss at 24 months in normal tissue complication probability (NTCP) modeling studies [10]. The risk of radiation-induced hearing impairment largely depends on tumor location, especially when involving the posterior fossa, sella, or basal temporal lobe. The only evidence of benefit of PBT in this context is a dose-modelling study by Dennis et al., which demonstrated that passive-scanning PBT reduced NTCP by 5–10% for the cochlea and 4% for the pituitary gland in adults with low-grade gliomas [42].

Proton beam therapy clearly offers superior dose conformity and delivers a lower total integral dose to surrounding tissues due to its physical properties. The assumption that PBT can reduce toxicity is supported by substantial evidence of a dose-response relationship for many radiation-induced toxicities. However, despite the dosimetric advantages of proton therapy, the extent of its clinical benefit in adult patients remains uncertain, especially in adults. Age at the time of radiation has been identified as one of the most important predictors of cognitive and endocrine outcomes [18, 33]. The evidence gathered in the pediatric population for proton therapy should not be directly extrapolated to adult patients as the impact of neurocognitive decline post-radiation is often less pronounced in adults. Therefore, a randomized trial comparing standard-of-care IMRT with IMPT in adults receiving partial brain radiotherapy is highly desirable. Ongoing trials with similar designs often include a single histological diagnosis, such as low-grade glioma or cavernous hemangioma, providing high-quality evidence of PBT in the forthcoming years (Table 2) [43, 44]. However, we believe a basket trial including mixed histologies with good prognosis will facilitate recruitment and also offer an answer to the common endpoint of functional preservation, which is primarily influenced by factors such as patient age, tumor location, use of chemotherapy, and radiotherapy dose, leading to more generalized applicability of PBT in clinical practice. Since these variables will be incorporated as stratification factors during randomization, the results should remain interpretable and clinically meaningful.

Table 2 Ongoing randomized controlled trials of proton beam therapy in adults with primary brain tumors

Study	Population	Sample size	Arms	Primary Endpoint	Timeline
NRG BN-005 (NCT03180502)	IDH mutant low-intermediate grade gliomas	120	IMPT vs. IMRT	Neurocognition	Accrual completed in March 2024
PRO-GLIO (NCT05190172)	IDH mutant grade 2–3 gliomas	225	IMPT vs. IMRT	2-year first intervention-free survival	Expected accrual completion in 2027
COG-PROTON-01 (NCT05895344)	Grade 1 Cavernous sinus meningiomas	160	IMPT vs. IMRT	5-year neurocognitive outcomes	Expected completion in 2032
APPROACH (ISRCTN:13390479)	Oligodendroglioma	246	IMPT Vs IMRT	5-year neurocognitive function	Accrual completion expected in 2027
Current study (PRIDE) (NCT06831461)	Primary brain tumors with expected survival > 5 years	156	VMAT vs. IMPT	5-year functional survival (composite endpoint)	Expected completion 2032

Post-radiation functional impairments are multifactorial, with several other factors besides radiation dose influencing outcomes. Reported rates of radiation-related toxicities with photon therapy vary widely due to confounding factors, making it difficult to establish a standard historical control as a comparator. Most studies have attempted to capture the differential benefit of proton therapy in specific functional domains, but we believe that each functional impairment—whether in cognition, hormonal balance, hearing, or performance status—constitutes a clinically meaningful event that impacts QoL. Therefore, we propose using a composite endpoint for efficacy analysis, a similar approach to that adopted in the ongoing IMPROVE-CODEL trial [45]. This approach allows for exploring the relevant benefits of proton therapy and accounts for toxicity and tumor control.

Proton beam therapy (PBT) is a relatively expensive form of radiation therapy (RT), and concerns about its cost remain at the forefront [46]. The cost of proton therapy varies globally, impacting either the patient or the healthcare system. This emphasizes the need for a clear understanding of the clinical utility of proton therapy and its potential to offer meaningful benefits. Currently, along with cost, the availability of proton therapy is limited. However, the use of PBT is constantly increasing, with new facilities opening worldwide. As the technology matures, long-term costs relative to photon therapy may decrease as demand grows and the longer life cycle of PBT machines compared to linear accelerators becomes evident [16].

Conclusion

The PRIDE study is an open-label, phase 3 randomized controlled trial designed to assess whether proton therapy offers superior neurological functional preservation compared to photon therapy in adults with primary brain tumours. Patients aged 18–70 years undergoing focal cranial radiotherapy with conventional fractionation are randomized to either the standard arm (IMRT) or the experimental arm (PBT). The primary endpoint is the 5-year rate of overall survival without functional deterioration (functional survival). Secondary endpoints include specific domains of functional survival such as neurocognitive decline, ototoxicity, endocrine dysfunction, overall and progression-free survival, and quality of life. If proven superior, the trial will provide level 1 evidence supporting the clinical use of proton therapy in adults with supratentorial brain tumors and a favourable prognosis.

Abbreviations

RT	Radiotherapy
IMRT	Intensity Modulated Radiotherapy
QoL	Quality of life
PBT	Proton Beam therapy
OAR	Organs at risk
CNS	Central Nervous System
IDH	Isocitrate dehydrogenase
VMAT	Volumetric modulated arc therapy
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume
TPS	Treatment planning system
ALARA	As low as reasonably achievable
CTCAE	Common Terminology Criteria for Adverse Events
FSIQ	Full Scale Intelligence Quotient
VQ	Verbal Quotient
PQ	Performance Quotient
IGF	Insulin-like growth factor
GH	Growth hormone
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
EORTC	European Organisation for Research and Treatment of Cancer
PSQI	Pittsburgh Sleep Quality Index
MADRE	Mannheim Dream questionnaire
RANO	Response Assessment in Neuro-Oncology
fS	Functional Survival
OS	Overall survival
PFS	Progression free survival
MRI	Magnetic resonance imaging
PET	Positron emission tomography
IMPT	Intensity modulated proton therapy
BBB	Blood brain barrier
SNHL	Sensorineural hearing loss
NTCP	Normal tissue complication probability

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Author contributions
Study concept and design: Archya Dasgupta, Tejpal Gupta, Suman Ghosh. Study conduct and data collection: All authors. Statistical analysis: Sadhana Kannan, Archya Dasgupta, Tejpal Gupta, Writing manuscript and approval: All authors. Funding acquisition: Archya Dasgupta Study administration: Archya Dasgupta.

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Data availability
Data will be provided upon reasonable request to the principal investigator, following the guidelines by the institutional ethics committee.

Declarations

Ethics approval and consent to participate
The study is being conducted in accordance with ICMR (2017) "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, Good Clinical Practice and the principles of the Declaration of Helsinki. The study, including all the study-related documents, has obtained approval from the Ethics Committee prior to the enrolment of participants. The trial has been registered with the Clinical Trial Registry of India (CTRI/2025/03/082568 dated 18.03.2025) and Clinicaltrials.gov (study identifier NCT06831461 dated 18.02.2025).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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