Proton therapy and limited surgery for paediatric and adolescent patients with craniopharyngioma (RT2CR): a single-arm, phase 2 study

Thomas E Merchant, Mary Ellen Hoehn, Raja B Khan, Noah D Sabin, Paul Klimo, Frederick A Boop, Shengjie Wu, Yimei Li, Elizabeth A Burghen, Niki Jurbergs, Eric S Sandler, Philipp R Aldana, Daniel J Indelicato, Heather M Conklin

Summary

Background Compared with photon therapy, proton therapy reduces exposure of normal brain tissue in patients with craniopharyngioma, which might reduce cognitive deficits associated with radiotherapy. Because there are known physical differences between the two methods of radiotherapy, we aimed to estimate progression-free survival and overall survival distributions for paediatric and adolescent patients with craniopharyngioma treated with limited surgery and proton therapy, while monitoring for excessive CNS toxicity.

Methods In this single-arm, phase 2 study, patients with craniopharyngioma at St Jude Children's Research Hospital (Memphis TN, USA) and University of Florida Health Proton Therapy Institute (Jacksonville, FL, USA) were recruited. Patients were eligible if they were aged 0–21 years at the time of enrolment and had not been treated with previous radiotherapeutic or intracystic therapies. Eligible patients were treated using passively scattered proton beams, 54 Gy (relative biological effect), and a 0·5 cm clinical target volume margin. Surgical treatment was individualised before proton therapy and included no surgery, single procedures with catheter and Ommaya reservoir placement through a burr hole or craniotomy, endoscopic resection, trans-sphenoidal resection, craniotomy, or multiple procedure types. After completing treatment, patients were evaluated clinically and by neuroimaging for tumour progression and evidence of necrosis, vasculopathy, permanent neurological deficits, vision loss, and endocrinopathy. Neurocognitive tests were administered at baseline and once a year for 5 years. Outcomes were compared with a historical cohort treated with surgery and photon therapy. The coprimary endpoints were progression-free survival and overall survival. Progression was defined as an increase in tumour dimensions on successive imaging evaluations more than 2 years after treatment. Survival and safety were also assessed in all patients who received photon therapy and limited surgery. This study is registered with ClinicalTrials.gov, NCT01419067.

Findings Between Aug 22, 2011, and Jan 19, 2016, 94 patients were enrolled and treated with surgery and proton therapy, of whom 49 (52%) were female, 45 (48%) were male, 62 (66%) were White, 16 (17%) were Black, two (2%) were Asian, and 14 (15%) were other races, and median age was 9·39 years (IQR 6·39–13·38) at the time of radiotherapy. As of data cutoff (Feb 2, 2022), median follow-up was 7·52 years (IQR 6·28–8·53) for patients who did not have progression and 7·62 years (IQR 6·48–8·54) for the full cohort of 94 patients. 3-year progression-free survival was 96·8% (95% CI 90·4–99·0; p=0·89), with progression occurring in three of 94 patients. No deaths occurred at 3 years, such that overall survival was 100%. At 5 years, necrosis had occurred in two (2%) of 94 patients, severe vasculopathy in four (4%), and permanent neurological conditions in three (3%); decline in vision from normal to abnormal occurred in four (7%) of 54 patients with normal vision at baseline. The most common grade 3–4 adverse events were headache (six [6%] of 94 patients), seizure (five [5%]), and vascular disorders (six [6%]). No deaths occurred as of data cutoff.

Interpretation Proton therapy did not improve survival outcomes in paediatric and adolescent patients with craniopharyngioma compared with a historical cohort, and severe complication rates were similar. However, cognitive outcomes with proton therapy were improved over photon therapy. Children and adolescents treated for craniopharyngioma using limited surgery and post-operative proton therapy have a high rate of tumour control and low rate of severe complications. The outcomes achieved with this treatment represent a new benchmark to which other regimens can be compared.

Funding American Lebanese Syrian Associated Charities, American Cancer Society, the US National Cancer Institute, and Research to Prevent Blindness.

Lancet Oncol 2023; 24: 523–34

Published Online April 18, 2023 https://doi.org/10.1016/S1470-2045(23)00146-8

See Comment page 422

Department of Radiation Oncology (T E Merchant DO, E A Burghen PNP), **Department of Surgery** (M E Hoehn MD, P Klimo MD, F A Boop MD), **Department of Pediatric Medicine** (R B Khan MD), **Department of Diagnostic Imaging** (N D Sabin MD), **Department of Biostatistics** (S Wu MS, Y Li PhD), **and Department of Psychology** (N Jurbergs PhD, H M Conklin PhD), **St Jude Children's Research Hospital, Memphis, TN, USA; Nemours Children's Health System, Jacksonville, FL, USA** (E S Sandler MD); **Department of Neurosurgery** (P R Aldana MD) **and Department of Radiation Oncology** (D J Indelicato MD), **University of Florida College of Medicine, Jacksonville, FL, USA**

Correspondence to: Dr Thomas E Merchant, Department of Radiation Oncology, St Jude Children's Research Hospital, Memphis, TN 38105-3678, USA **thomas.merchant@stjude.org**

Introduction

A craniopharyngioma is an intracranial tumour that predominantly presents in children with wide-ranging symptoms and catastrophic effects. Surgery and radiotherapy are the mainstays of treatment. Each method can be uniquely tailored to treat this locally aggressive

Research in context

Evidence before this study

We searched PubMed on July 1, 2011, for clinical trials published in English since Jan 1, 1988, using different combinations of the terms "craniopharyngioma", "radiotherapy", "pediatric", and "outcomes"; we also searched ClinicalTrials.gov using the same terms for clinical trials with posted results for children younger than 18 years treated for craniopharyngioma using proton radiotherapy. Our search found no published data describing outcomes for children and adolescents treated using proton radiotherapy and the estimated benefit of proton radiotherapy compared with photon radiotherapy.

Added value of this study

In this phase 2 study, we estimated the rate of tumour control in young patients with craniopharyngioma using passively scattered proton beams and 0·5 cm clinical target volume margin. We compared progression-free survival and overall survival to a historic cohort treated using photon radiotherapy. We found no difference between the two methods in terms of survival or incidence of severe complications. To our knowledge, this study is one of the first prospective studies involving paediatric and adolescent patients with a single tumour type to show an advantage of proton beam therapy in terms of cognitive outcomes with long-term follow-up. The study provides a model approach to assess newer methods of radiotherapy in the treatment of childhood brain tumours and highlights the need for rigorous and long-term follow-up.

Implications of all the available evidence

These results could be practice changing if they convince caregivers to recommend proton beam therapy over radical surgery or the referral of patients for proton beam therapy instead of radiotherapy using photons. Health-care systems have invested substantial resources to acquire access to advanced radiation-therapy methods hoping for convincing evidence of a benefit of proton beam therapy. Public health-care agencies promoting universal access and health equity should weigh the available evidence on the benefits, risks, and cost-effectiveness of new and established treatments to support referral of patients with rare conditions such as craniopharyngioma for treatment with proton beam therapy.

midline tumour that is intimately associated with the visual pathways, hypothalamic–pituitary axis, and central components of the cerebral vasculature.[1]

For newly diagnosed patients, decisions to use radical surgery or limited surgery and definitive irradiation are driven by institutional preferences and experiences. The low incidence of this tumour restricts experience in treatment for most centres and affects establishment of a standard of care.[2,3]

Most children treated in the USA for craniopharyngioma receive fractionated external beam radiotherapy at the time of initial diagnosis or progression after radical resection. The use of unsealed radioactive sources or chemotherapy to treat tumour cysts, single-fraction radiosurgery to treat limited-volume residual tumour, and hypofractionated radiotherapy regimens have been selectively applied to small cohorts or in the setting of recurrence after conventional irradiation.[4,5]

Craniopharyngioma has several features that make it amenable to advanced methods of targeting, localisation, and external beam delivery. These features include the deep, central intracranial locations and generally distinct borders. When treating children, normal tissue sparing, achieved by reducing target volume margins or the use of advanced methods, has been a priority, whereas total dose and fractionation regimens have remained largely unchanged.[6]

See Online for appendix

We designed the RT2CR trial to estimate the progression-free survival and overall survival distributions for children and adolescents with craniopharyngioma treated with limited surgery and proton therapy using a 0·5 cm clinical target volume margin while monitoring for excessive necrosis of the CNS, clinically important vasculopathy, and permanent neurological conditions or deficits.

Methods

Study design and participants

In this single-arm, phase 2 study, patients diagnosed with craniopharyngioma by histology, intraoperative assessment, or neuroimaging confirmed at St Jude Children's Research Hospital (Memphis TN, USA) were eligible for inclusion and recruited. Patients were eligible if they were aged 12 months to 21 years at the time of enrolment and had not previously been treated with radiotherapy or intracystic therapies. Pregnant women were excluded because proton therapy has the potential for teratogenic or abortifacient affects. The cost of proton treatment was covered by private or public health insurance or St Jude Children's Research Hospital. No patient or family were required to pay for care or ancillary clinical or research-related expenses. Protocol-related expenses were entirely supported by St Jude Children's Research Hospital.

The protocol (appendix) and consent documents were approved by the Institutional Review Boards of St Jude Children's Research Hospital and the University of Florida Health Proton Therapy Institute (Jacksonville, FL, USA).

The outcomes from the proton cohort were compared with a historical cohort of 101 paediatric and adolescent patients with craniopharyngioma enrolled on or treated according to a phase 2 single institutional protocol[12] (NCT00187226) after 1998. Between

April, 1998, and December, 2013, 101 children and adolescents aged 3–17 years were treated with photon-based conformal or intensity-modulated radiation therapy at St Jude Children's Research Hospital. 76 children and adolescents were enrolled on a phase 2, single institutional protocol beginning in 1998, or followed a non-protocol treatment plan (n=25). Surgery was individualised and 54 Gy radiation was administered using a 1 cm or 0·5 cm clinical target volume margin. Median age at the time of conformal photon radiotherapy was 9·50 years (range 3·20–17·63). Patients were followed for 10 years with serial magnetic resonance imaging and magnetic resonance angiography and a battery of tests to assess hearing, vision, hormone deficiencies, and cognitive performance. Median follow-up for survivors was 14·94 years (range 7·23–21·5).[7–9]

Procedures

There was no limit to the number of surgical procedures that could be done before proton therapy. Many initial operations were completed by the referring teams. The first tumour-directed surgery was performed at the enrolling institutions in 20 patients and a total of 33 patients had a tumour-directed surgery at the enrolling institutions before irradiation. Patients were grouped according to surgery type—ie, no surgery, transsphenoidal surgery, closed (burr hole) placement of catheter and Ommaya reservoir, open (craniotomy) placement of catheter and Ommaya reservoir, endoscopic surgery via burr hole, craniotomy, or several approaches.

Conformal proton therapy was administered using passive scattering methods with apertures and compensators. The gross tumour volume was defined as the postoperative tumour bed and residual tumour, the clinical target volume included an anatomically defined margin of 0·5 cm surrounding the gross tumour volume, and the planning target volume was a geometric margin of 0·3 cm surrounding the clinical target volume. The clinical target volume was intended to include subclinical microscopic disease. The planning target volume was meant to account for variation in daily treatment, beam uncertainties, and aperture design. Proton-specific uncertainties were accounted for in the design of each proton beam. For recording and reporting purposes, a generic planning target volume was constructed from the clinical target volume with a uniform expansion equal to the lateral setup margins. The prescribed total dose was 54 Gy (relative biological effect [RBE]) using conventional fractionation of 1·8 Gy (RBE) per day. Once a week non-contrast MRI was done to monitor for changes in the target volume that would require replanning.

As previously reported,[7] the clinical target volume margins for the comparison photon cohort were 1·0 cm in the first 25 patients in the photon cohort, which was reduced to a margin of 0·5 cm or less for the remaining patients in the cohort as conformal methods were improved. Planning target volume margins for patients in the photon cohort ranged from 0·5 cm for the patients enrolled before Jan 24, 2007, to 0·3 cm for those treated using image guidance after Jan 24, 2007.

Patients were assessed by a multidisciplinary team at baseline. A physical examination was timed to match imaging assessments that were done every 3 months, dated from the start of treatment up to 12 months after treatment, followed by evaluations twice per year up to year 5 after the start of treatment, and once per year thereafter. Magnetic resonance angiography (MRA) was done at baseline and at the time of annual surveillance imaging evaluation. Occurrences of severe stenosis were further evaluated with cerebral angiography. Additional treatment with aspirin was allowed at the discretion of the treating physician. The trial was a collaborative effort between St Jude Children's Research Hospital and the University of Florida Health Proton Therapy Institute. Baseline and follow-up protocol evaluations were done at St Jude Children's Research Hospital. Proton therapy was administered at the University of Florida Health Proton Therapy Institute. Information about ophthalmology assessments are in the appendix (p 3).

Progression was defined as an increase of 25% or more in the perpendicular tumour dimensions on two or more successive imaging evaluations beginning 2–3 years after treatment. The progression date was the date at which increase in tumour dimensions was first detected. We used the Common Terminology Criteria for Adverse Events (version 4.0) to assess adverse events as part of the routine clinical evaluation process. Grade 3 and 4 adverse events were reported to the institutional review board.

Neuropsychological assessments were done at baseline and repeated once per year for 5 years. Intellectual functioning was assessed using the age-appropriate Wechsler scale, with derivation of a full-scale intelligence quotient (FSIQ).[10,11] Adaptive functioning, or self-care skills, was assessed using a parent report on the Adaptive Behavior Assessment System, second edition.[12] Parent reports were used for patients older than 18 years of age. The photon comparison group also participated in annual neuropsychological assessments that included the age-appropriate Wechsler scale.[13,14] For both cohorts, derivation of FSIQ or estimated intelligence quotient (EIQ) depending on the timepoint; FSIQ and EIQ were combined to maximise data for analysis. In the photon cohort, patients' parents provided reports of adaptive functioning using the Vineland Adaptive Behavior Scales. Similar to the proton cohort, parent reports were used for those older than 18 years of age.[15] All measures were considered to be the gold standard for the field and scores were age standardised using large, representative normative samples. All age-standarised scores had a mean of 100 and SD of 15; higher scores indicated better performance.

Outcomes

The primary objective of the RT2CR protocol was to estimate the progression-free survival and overall survival for children and young people with craniopharyngioma treated with limited surgery and proton therapy using a 0·5 cm clinical target volume margin, while monitoring for excessive necrosis of the CNS, clinically important vasculopathy, and permanent neurological conditions or deficits. Progression-free survival was defined from the start of radiotherapy to the first sign of progression. The secondary objectives were to estimate the cumulative incidence of cystic intervention and the event-free survival distribution, and to compare the distributions of progression-free survival, event-free survival, and overall survival to those of an historic cohort treated with photon therapy. The cumulative incidence of cystic interventions will be reported separately. Event-free survival, defined as tumour progression or death unrelated to tumour progression was not reported for there were no deaths recorded among the patients treated on the study.

The trial was also designed to estimate the distributions of progression-free survival and overall survival for children and young people with craniopharyngioma treated only with primary surgical resection, and to compare these distributions with the distributions observed for patients treated with limited surgery and proton therapy. Seven patients were enrolled who were treated only with primary surgical resection, and were not included in the current analysis.

Exploratory objectives included investigation of potential associations of clinical and treatment factors with the incidence and severity of neurological, endocrine, and cognitive deficits and descriptively comparing findings for the proton therapy cohort with the photon therapy cohort. Additional exploratory objectives to be reported elsewhere include investigations of the sleep quality, fatigue, and quality of life of patients in the proton cohort; their physical performance and movement; the incidence and severity of structural, functional, and vascular effects of the treatment on healthy brain tissue; growth factor and cytokine responses; and exploratory genetic analyses to better understand the biology that underlies craniopharyngioma, treatment response, and various side-effects. A complete list of the primary, secondary, and exploratory objectives is in the appendix (p 6).

Statistical analysis

We compared long-term disease control and outcome data between the proton and the photon cohort. The 5-year progression-free survival, 5-year overall survival, and their 95% CIs were estimated using the Kaplan-Meier method. A log-rank test was used to compare survival distributions between the proton cohort and the photon cohort. A one-sided binomial test was prespecified and used to test whether the 3-year progression-free survival rate in the proton group was lower than in the photon group, the primary outcome of the trial. For the survival analysis, we included all patients in the proton cohort who had both proton therapy and limited surgery, excluding any who only had surgery. We calculated 5-year cumulative incidences (and 95% CIs) of necrosis, vasculopathy, and permanent neurological deficits unrelated to necrosis or vasculopathy, and disease progression or death were treated as competing events if they occurred before the events of interest. Gray's method was used to compare the cumulative incidences between the two cohorts. The estimated cumulative incidence with SE were reported. A linear mixed model was used to investigate changes in neurocognitive scores over time. Cerebrospinal fluid (CSF) shunting was used as a proxy for hydrocephalus when evaluating the effects of clinical covariates on neurocognitive scores. The χ^2 test was used to investigate the association between of categorical variables. Student's *t* test was used to compare continuous variables. All aforementioned analyses were prespecified in the protocol. Additionally, post hoc we estimated hazard ratios (HR) and 95% CIs between the proton and photon cohorts for progression-free survival using the Cox regression method. All analyses were done using SAS version 9.4.

The study was originally designed to include 140 patients, accounting for ineligible patients, such that only 130 patients were intended to be analysed for objectives, comprising two groups: the proton therapy group (n=105) and observation after radical surgery (ie, gross-total resection) group (n=25) strata. Only the proton therapy group was included in this Article because the observation group did not accrue the planned number of patients and meaningful comparisons were not possible. The original statistical design developed before the activation of the study in 2011 used available data from 93 patients who underwent photon therapy. This study was not designed as a non-inferiority trial, but as a single-arm study and the statistical design was based on a binary endpoint to have 91·0% statistical power (one-sided test α=0·05) to detect a decrease in the 3-year progression-free survival rate from 94·6% to 86·0%, chosen on the basis of the 3-year progression-free survival rate of an historical photon cohort.[7] The study was stopped early after enrolling 94 patients in the proton therapy group when a newer method of proton therapy became available. We did a post-hoc power analysis using 94 patients instead of the planned 101 patients. The revised power analysis showed 89·1% power instead of 91·0% power to detect the 3-year progression-free survival rate difference and the null hypothesis was that H_0 would be: p=0·946 and *vs* H_a: would be p<0·946, where p is the one-sided binomal p value for the 3-year progression-free survival.

This study is registered with ClinicalTrials.gov, NCT01419067.

Role of the funding source

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

Results

Between Aug 22, 2011, and Jan 19, 2016, 94 patients were enrolled into the proton cohort, and from Sept 19, 2011, to Feb 22, 2016, the same number started proton therapy. 49 (52%) of 94 were female, 45 (48%) were male, 62 (66%) were White, 16 (17%) were Black, two (2%) were Asian, and 14 (15%) were other races, and median age was 9·39 years (IQR 6·39–13·38) at the time of radiotherapy (table 1). As of data cutoff (Feb 2, 2022), median follow-up was 7·62 years (IQR 6·48–8·54) and nine (10%) of 94 patients had had tumour progression, with median time from start of radiotherapy to progression of 3·09 years (IQR 2·05–5·06). Among patients without progression, median follow-up was 7·52 years (IQR 6·28–8·53). We compared outcomes for the patients undergoing proton therapy with a cohort of 101 patients treated using photon therapy, with a median follow-up of 13·25 years (9·43–16·65) after photon therapy. Baseline demographic and clinical characteristics and treatment characteristics for the proton and photon therapy cohorts are shown in table 1 and in the appendix (pp 4–5). All patients in the proton therapy cohort completed proton therapy and received the protocol-specified dose of 54 Gy (RBE). The median number of elapsed days from proton radiotherapy start to completion was 42 (range 39–49). Cyst expansion required replanning in eight patients, cyst drainage in four patients, and both replanning and cyst drainage in two patients (detailed information about the type and number of surgery procedures by cohort is presented in the appendix pp 4–5).

In the proton therapy cohort, 3-year progression-free survival was 96·8% (95% CI 90·4–99·0; three progression events) and 5-year progression-free survival was 93·6% (86·3–97·1; nine progression events figure 1A). Median progression-free survival was not reached. The one-sided binomial test showed that there was no statistical evidence of a decline in 3-year progression-free survival (p=0·89). There were no deaths during the study for the proton cohort, such that 3-year and 5-year overall survival was 100%. There was no statistical evidence to show that 3-year progression-free survival using proton therapy was lower than that of photon therapy. Similarly, there was no difference when comparing progression-free survival and overall survival at 5 years (figure 1B). The HR for progression-free survival over 5 years was HR 0·54 (95% CI: 0·24–1·19; post hoc)

Two (2%) of 94 patients in the proton therapy cohort had necrosis of the CNS, one at 3·9 months and the other at 7·4 months after the initiation of radiotherapy (figure 2A). Both had imaging evidence of cerebral ischaemia after their initial surgery, and both were treated successfully for necrosis with hyperbaric oxygen therapy. Two (2%) of 101 patients in the photon cohort developed necrosis, one at 4·7 months and one at 5·8 months after starting radiotherapy (figure 2A). There was no difference in cumulative incidence between the two cohorts, as shown by Gray's method (appendix p 2).

	Photon therapy cohort (n=101)	Proton therapy cohort (n=94)	p value
Follow-up, years	14·70 (12·18–17·27)	6·62 (6·48–8·54)	..
Age at time of radiotherapy, years	8·98 (6·31–13·02)	9·39 (6·39–13·38)	0·52
Sex			
Female	46 (46%)	49 (52%)	0·39
Male	55 (54%)	45 (48%)	..
Race			
Asian	1 (1%)	2 (2%)	<0·0001*
Black	22 (22%)	16 (17%)	..
Hispanic	2 (2%)	0	..
Mixed	0	14 (15%)	..
White	76 (75%)	62 (66%)	..
CFS shunt			
No	74 (73%)	88 (94%)	0·0002
Yes	27 (27%)	6 (6%)	..
Total number of tumour-directed procedures before radiotherapy	197†	140‡§	0·0019
Surgery			
Two or more procedures	46 (46%)	31 (33%)	0·16
One procedure	50 (10%)	59 (63%)	..
None	5 (5%)	4 (4%)	..
Mean radiation dose (Gy)			
Brain	16·89 (14·46–18·79)	8·79 (6·74–10·61)	<0·0001
Temporal left	18·70 (13·87–21·52)	7·99 (5·60–10·62)	<0·0001
Temporal right	18·51 (14·17–22·49)	7·99 (5·60–10·76)	<0·0001

Data are presented as n (%) or median (IQR). Percentages might add up to more than 100% due to rounding. CSF=cerebrospinal fluid. *Race was a characteristic that was not balanced between treatment groups (p<0·0001). When the race categories Black and White were compared, there was no difference between protocols (p=0·8543). †Occurring in 96 patients undergoing photon therapy. ‡Occurring in 90 patients undergoing proton therapy. §The first tumour-directed surgery was done at enrolling institutions in 20 patients and 33 patients had a tumour-directed surgery at their enrolling institutions before irradiation.

Table 1: **Baseline patient and treatment characteristics for photon and proton therapy cohorts**

Five (5%) of 94 patients in the proton therapy cohort had pre-existing vasculopathy. Two (40%) of these five patients developed severe vasculopathy and required revascularisation. After proton therapy, seven (7%) of 89 remaining patients developed vasculopathy (figure 2B). Four (57%) of seven patients had severe vasculopathy (figure 2C) and three (43%) had moderate vasculopathy. Severe vasculopathy was characterised by abnormal cerebral angiogram, uncompensated perfusion MRI, and revasculisation surgery. Patients with moderate vasculopathy who had severe stenosis on the basis of MRA findings that were confirmed by cerebral angiography;

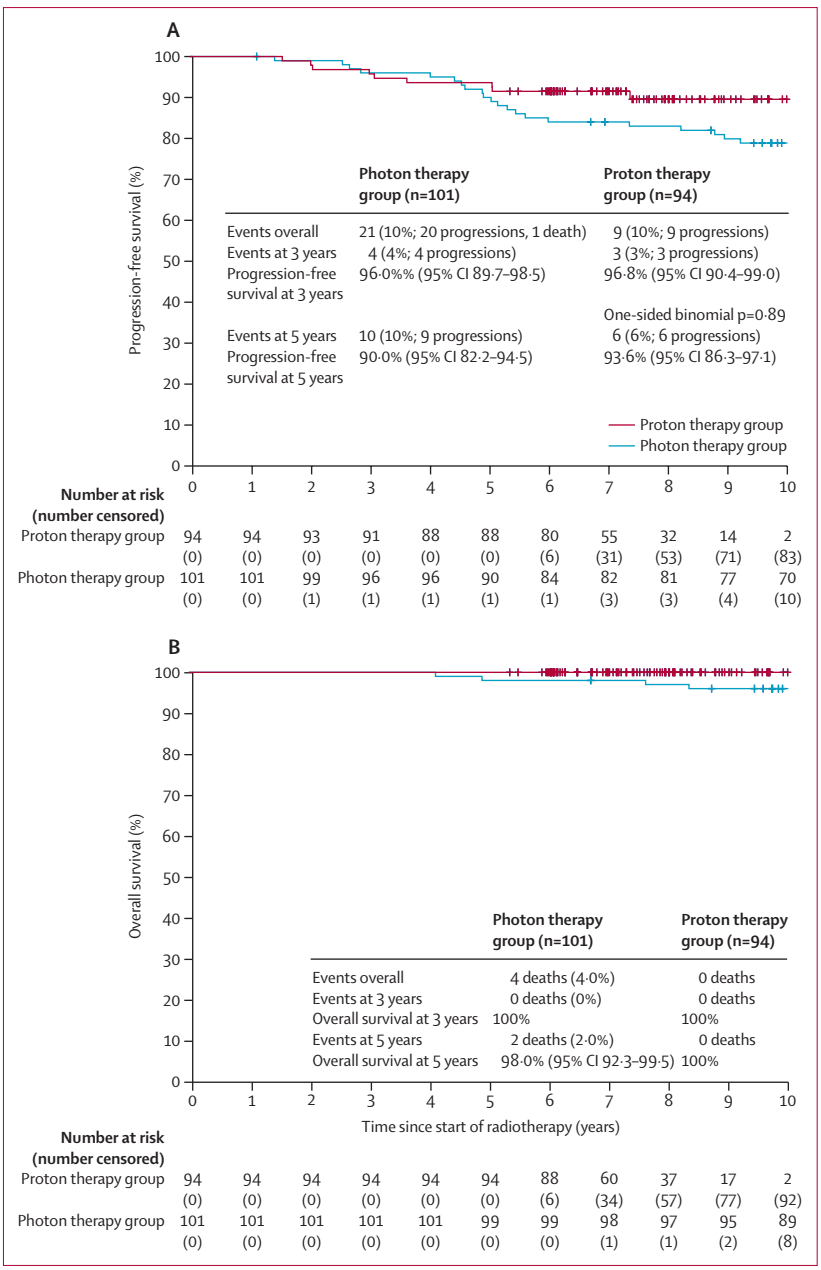


Figure 1: **Progression-free survival (A) and overall survival (B)**
In the proton therapy cohort, 3-year progression-free survival was 96·8% (95% CI 90·4–99·0) and 5-year progression-free survival was 93·6% (86·3–97·1). In the photon therapy cohort, 3-year progression-free survival was 96·0% (95% CI 89·7–98·5) and 5-year progression-free survival was 90·0% (82·2–94·5). The number of events for progression-free survival at 5 years was 6 (6%) of 94 for proton and 10 (10%) of 101 for photon. Progression was defined as an increase of 25% or more in the perpendicular tumour dimensions on two or more successive imaging evaluations 2–3 years after treatment and the date recorded as the earliest site of increase in tumour dimensions.

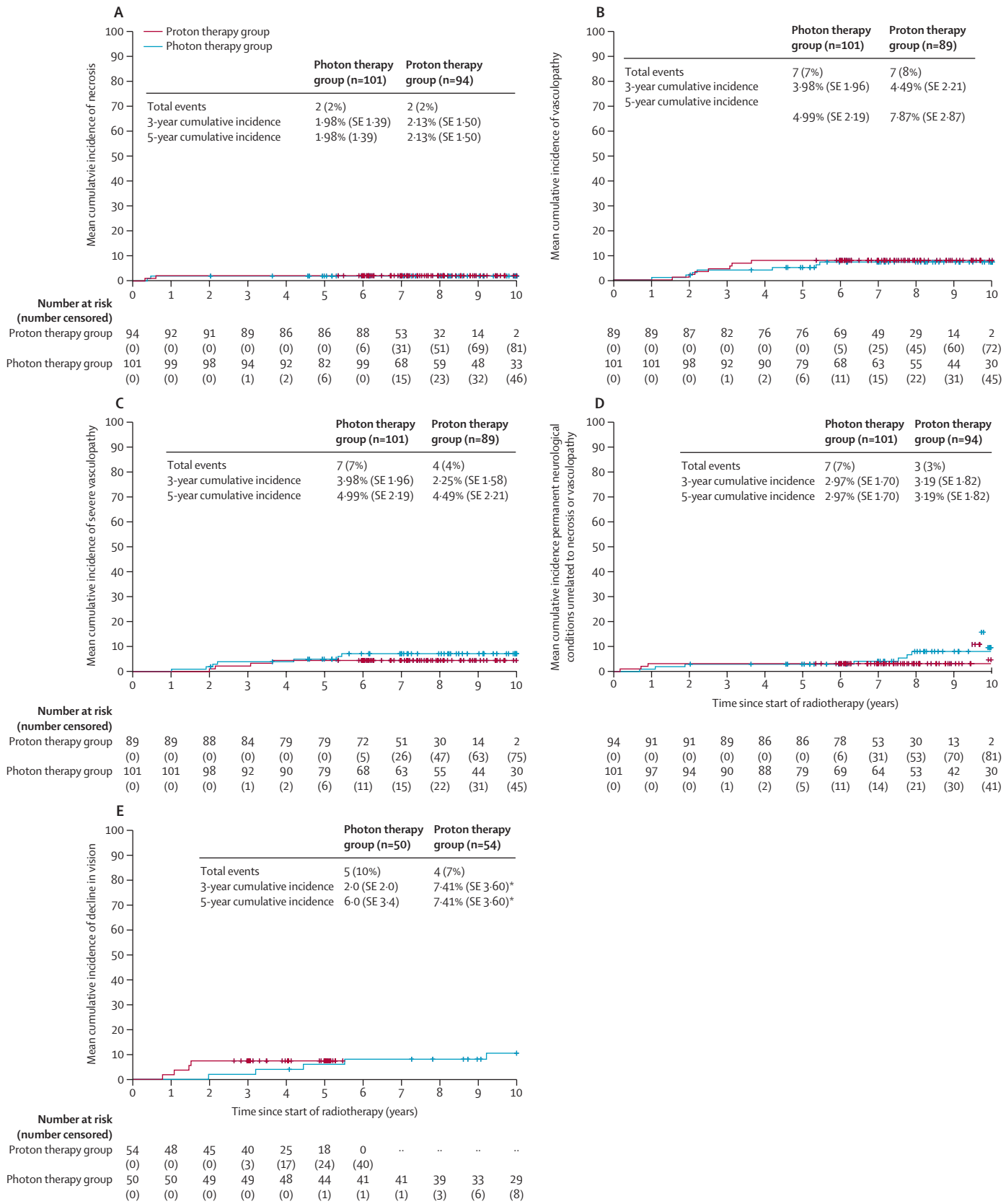
however, they had evidence of compensation of perfusion deficits on MRI perfusion studies. All patients who had any severity of vasculopathy were treated with low-dose (81 mg once per day) aspirin therapy at the discretion of the treating physician. Two of 89 patients who had MRA evidences of severe stenosis who underwent magnetic

Figure 2: **Cumulative incidence of necrosis (A), vasculopathy (B), severe vasculopathy (C) , permanent neurological conditions unrelated to necrosis or vasculopathy (D), and change from normal vision to abnormal vision (E)***
For panels B and C, the five patients in the proton therapy cohort who had pre-existing vasculopathy were not included in the plots. Results are corrected for change in visual field assessment from confrontational testing to automated static perimetry (E). *Excluding decline discovered when transitioning from confrontational to Humphrey visual field testing in younger patients, and temporally associated tumour progression.

resonance perfusion and did not show deficits. These patients did not have a cerebral angiography. Cumulative incidence of vasculopathy and severe vasculopathy for the photon cohort is shown in figure 2B and C). Time to vasculopathy and severe vasculopathy is in the appendix (p 3).

Three (3%) of 94 patients in the proton therapy cohort and three (3%) of 101 in the photon therapy cohort developed permanent neurological conditions unrelated to necrosis or vasculopathy are shown in figure 2D. Permanent neurological conditions in the proton therapy group included paraesthesia, basal ganglia syndrome, and dystonia (one patient each; figure 2). Time to each event in each cohort is shown in the appendix (p 3).

At 5 years, 818 ophthalmology evaluations were available for 94 patients in the proton therapy cohort through the time of analysis. 54 (57%) of 94 patients had normal visual acuity and visual field at baseline. At the last follow-up, any visual field deficit was observed in ten (19%) of 54 patients and a decline in visual acuity to the level of monocular impairment was observed in one (2%) of 54 patients. The mean cumulative incidence of decline was 18·52% (SD 5·34) at 3 years and 20·86% (5·69) at 5 years. When excluding decline discovered when transitioning from confrontational to Humphrey visual field testing in younger patients, and temporally associated tumour progression (appendix p 3), mean cumulative incidence was 7·41% (3·60) at both the 3-year and 5-year timepoints (figure 2E). Optic atrophy was not associated with change in vision. Among the 40 patients with abnormal vision before proton therapy, mean cumulative incidence of improvement was 25·00% (SD 6·95) at 3 years and 27·50% (7·17) at 5 years. Visual acuity remained largely stable or improved for patients with normal or impaired vision at the start of treatment. 7 (14%) of 50 patients with normal visual acuity in the photon cohort has visual decline. Mean cumulative incidence of decline was 6·04% (3·42) for the photon cohort with a median follow-up for survivors of 14·94 years (range 7·23–21·5 years). Only one patient was followed for less than 10 years. Four (7%) of 54 patients with normal vision in the proton therapy cohort developed visual impairment with long-term follow-up, and in the photon therapy group, five (10%) of 50 patients at 10 years follow-up and three (6%) of 50 patients at 5 years follow-up developed visual impairment.


A
Proton therapy group
Photon therapy group
Mean cumulatvie incidence of necrosis
Photon therapy group (n=101)
Proton therapy group (n=94)
Total events 2 (2%) 2 (2%)
3-year cumulative incidence 1·98% (SE 1·39) 2·13% (SE 1·50)
5-year cumulative incidence 1·98% (1·39) 2·13% (SE 1·50)
Number at risk (number censored)
Proton therapy group 94 92 91 89 86 86 88 53 32 14 2
(0) (0) (0) (0) (0) (0) (6) (31) (51) (69) (81)
Photon therapy group 101 99 98 94 92 82 99 68 59 48 33
(0) (0) (0) (1) (2) (6) (0) (15) (23) (32) (46)
B
Mean cumulative incidence of vasculopathy
Photon therapy group (n=101)
Proton therapy group (n=89)
Total events 7 (7%) 7 (8%)
3-year cumulative incidence 3·98% (SE 1·96) 4·49% (SE 2·21)
5-year cumulative incidence 4·99% (SE 2·19) 7·87% (SE 2·87)
89 89 87 82 76 76 69 49 29 14 2
(0) (0) (0) (0) (0) (0) (5) (25) (45) (60) (72)
101 101 98 92 90 79 68 63 55 44 30
(0) (0) (0) (1) (2) (6) (11) (15) (22) (31) (45)
C
Mean cumulative incidence of severe vasculopathy
Photon therapy group (n=101)
Proton therapy group (n=89)
Total events 7 (7%) 4 (4%)
3-year cumulative incidence 3·98% (SE 1·96) 2·25% (SE 1·58)
5-year cumulative incidence 4·99% (SE 2·19) 4·49% (SE 2·21)
Number at risk (number censored)
Proton therapy group 89 89 88 84 79 79 72 51 30 14 2
(0) (0) (0) (0) (0) (0) (5) (26) (47) (63) (75)
Photon therapy group 101 101 98 92 90 79 68 63 55 44 30
(0) (0) (0) (1) (2) (6) (11) (15) (22) (31) (45)
D
Mean cumulative incidence permanent neurological conditions unrelated to necrosis or vasculopathy
Photon therapy group (n=101)
Proton therapy group (n=94)
Total events 7 (7%) 3 (3%)
3-year cumulative incidence 2·97% (SE 1·70) 3·19 (SE 1·82)
5-year cumulative incidence 2·97% (SE 1·70) 3·19% (SE 1·82)
Time since start of radiotherapy (years)
94 91 91 89 86 86 78 53 30 13 2
(0) (0) (0) (0) (0) (0) (6) (31) (53) (70) (81)
101 97 94 90 88 79 69 64 53 42 30
(0) (0) (0) (1) (2) (5) (11) (14) (21) (30) (41)
E
Mean cumulative incidence of decline in vision
Photon therapy group (n=50)
Proton therapy group (n=54)
Total events 5 (10%) 4 (7%)
3-year cumulative incidence 2·0 (SE 2·0) 7·41% (SE 3·60)*
5-year cumulative incidence 6·0 (SE 3·4) 7·41% (SE 3·60)*
Time since start of radiotherapy (years)
Number at risk (number censored)
Proton therapy group 54 48 45 40 25 18 0 .. ..
(0) (0) (0) (3) (17) (24) (40)
Photon therapy group 50 50 49 49 48 44 41 41 39 33 29
(0) (0) (0) (0) (0) (1) (1) (1) (3) (6) (8)

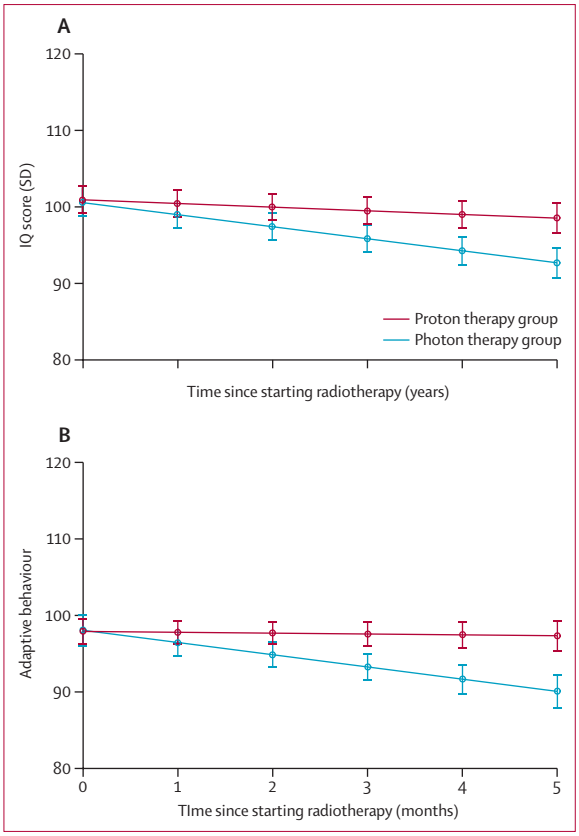


Figure 3: **Estimated mean values (SE) and modelled curves for longitudinal IQ (A) and adaptive behaviour (B) scores**

Neuropsychological assessments were done at baseline and repeated once per year for 5 years. IQ was assessed using the age-appropriate Wechsler scale (proton and photon cohorts) and adaptive functioning (adaptive behaviour), or self-care skills, was assessed using a parent report of the Adaptive Behavior Assessment System (proton cohort) and Vineland Adaptive Behavior Skills (photon cohort). A linear mixed model was used to estimate changes in scores over time. Mean estimates at the specific evaluation time points and modelled curves are presented. The differences in the curves were statistically significant IQ (1·094 points per year; p=0·0070) and adaptive behaviour (1·485 points per year; p=0·0303). IQ=intelligence quotient.

	Grade 1–2	Grade 3	Grade 4
Blood and lymphatic system disorders			
Anaemia	0	1 (1%)	0
Other blood and lymphatic system disorders	0	1 (1%)	0
Endocrine disorders			
Adrenal insufficiency	0	1 (1%)	0
Other endocrine disorders	0	1 (1%)	0
Eye disorders	0	0	1 (1%)
Gastrointestinal disorders			
Gastritis	0	1 (1%)	0
Other gastrointestinal disorders	0	3 (3%)	0
Vomiting	0	2 (2%)	0
Infections and infestations			
Catheter-related infection	0	1 (1%)	0
Device-related infection	0	1 (1%)	0
Sepsis	0	0	1 (1%)
Metabolism and nutrition disorders			
Dehydration	0	1 (1%)	0
Hypernatraemia	0	0	2 (2%)
Hyponatraemia	0	0	1 (1%)
Nervous system disorders			
Central nervous system necrosis	0	2 (2%)	0
Dysarthria	0	1 (1%)	0
Dysphasia	0	1 (1%)	0
Headache	17 (18%)	6 (6%)	0
Hydrocephalus	0	1 (1%)	0
Hypersomnia	0	1 (1%)	0
Other nervous system disorders	0	3 (3%)	0
Oculomotor nerve disorder	0	1 (1%)	0
Paresthesia	0	1 (1%)	0
Seizure	0	5 (5%)	0
Stroke	0	1 (1%)	0
Psychiatric disorders			
Other psychiatric disorders	0	1 (1%)	0
Psychosis	0	1 (1%)	0
Respiratory, thoracic, and mediastinal disorders			
Respiratory, thoracic, and mediastinal disorders	13 (14%)	1 (1%)	0
Surgical and medical procedures	0	2 (2%)	0
Vascular disorders			
Thromboembolic events	0	2 (2%)	0
Vascular disorders	0	6 (6%)	0

Data are for all grade 1–2 adverse events that occurred in at least 10% of patients, and all grade 3–5 adverse events. No patients had a grade 5 event, according to the CTCAE version 4.0.

Table 2: **Adverse events in the proton therapy cohort (n=94)**

Nine (10%) of 94 patients in the proton therapy group had diabetes insipidus at diagnosis and 45 (48%) acquired diabetes insipidus at surgery. None of the remaining 40 (43%) patients developed diabetes insipidus. At baseline assessment for proton therapy, growth-hormone deficiency was present in 70 (74%) of 94 patients, central hypothyroidism in 56 (60%) of 94, and central adrenal insufficiency in 59 (63%) of 94. Among the 101 patients in the photon therapy cohort, seven (7%) had diabetes insipidus at diagnosis and 47 (47%) acquired diabetes insipidus at surgery. None of the remaining 47 (47%) patients developed diabetes insipidus. When evaluated before photon therapy, growth-hormone deficiency was present in 30 (83%) of 36 patients who had available provocative testing and 21 (39%) of 54 who had available clinical factors and screening laboratory evaluation; nine (9%) of 101 patients were not tested because of logistical or medical reasons and two (2%) were previously prescribed growth-hormone replacement. Growth-hormone deficiency was confirmed or suspected in 53 (58%) of 92 patients in the photon therapy cohort with available laboratory data. Central hypothyroidism was present in 61 (60%) of 101 patients

and central adrenal insufficiency was present in 53 (53%) of 101. The 3-year and 5-year cumulative incidence of hypothyroidism, adrenal insufficiency, and hypogonadism was not significantly different between patients who had proton or photon therapy (appendix p 2).

Significant differences in longitudinal scores were observed with decreasing values for intelligence quotient (IQ; –1·09 points per year; p=0·0070) and adaptive behaviour (–1·48 points per year; p=0·030) in patients treated with photon therapy compared to those treated with proton therapy (figure 3). The estimated difference was 4·58 points over 5 years for IQ, and 7·34 points over 5 years for adaptive behaviour. When the dosimetry information was combined for all patients, the mean dose to the individual temporal lobes had a substantial effect on longitudinal change in IQ. For mean dose to the temporal left lobe, the decreasing rate over time was –0·066 points per Gy per year (p=0·014) after taking shunt and age at radiotherapy into account. For mean dose to the temporal right lobe, the decreasing rate over time was –0·074 points per Gy per year (p=0·0078) after taking shunt and age at radiotherapy into account. We included CSF shunting as a covariate in our analysis to represent a severe form of hydrocephalus. Baseline IQ scores were 10·8 points higher for patients with no CSF shunt (p=0·0037) when age and protocol cohort were included in the model of change in IQ over time. Baseline values for IQ on the basis of the model were 103·41 (SD 3·33) with no shunt versus 92·61 (4·46) with the presence of a shunt.

Grade 1–2 events recorded for more than 10% of patients were headache in 17 (18%) patients and respiratory disorders in 13 (14%) patients (table 2). The most common grade 3–4 adverse events were seizure (five (5%), headache (six [6%]), and vascular conditions (six [6%]). Ten serious adverse events (sepsis, hypernatraemia, hyponatraemia, headache, paraesthesia, and thromboembolic events) were reported in five patients. Five patients had a total of ten serious adverse events (one patient had an event of sepsis (grade 4), another patient had an event of paresthesia (grade 3), another patient had headache (grade 3), another patient had thromboembolic event (grade 3), and another patient had 5 events of hyperatraemia or hyponatraemia (grade 3–4).

Discussion

This study documents disease control in paediatric and adolescent patients with craniopharyngioma during the first 5 years after radiotherapy using passively scattered protons and shows similar tumour control compared with radiotherapy using photons. There was little doubt about the equivalence between the two radiation methods when the study was initiated. Passively scattered proton therapy provides a relatively uniform dose distribution across the targeted volume and the use of a planning target volume mitigated treatment-delivery uncertainties. Answering this fundamental question was required on the basis of the applied target volume definitions and the limited reported experience using proton therapy in children with this tumour type. Because of the small number of patients with progression after proton therapy in our study, further follow-up is required to definitively determine whether there is an association between clinical and treatment factors and outcomes. In our previous study,[16] we found that patients' race and permanent CSF shunting affected progression-free survival after photon therapy and the crucial need to monitor these patients with frequent imaging during treatment. However, these were not aspects we assessed here.

The trial was designed on the basis of our experience testing reduced target volume margins and the use of photon therapy.[17] When our models suggested that proton therapy, which reduces the volume of normal tissues exposed to intermediate or low doses,[18] might improve cognitive outcomes,[19] the current trial was proposed. Although proton therapy was considered the logical next step for children with craniopharyngioma, when the protocol was designed there were no clear guidelines for treatment planning and beam delivery (target volume margins, dose, and fractionation), and the radiobiological differences between photon and proton beams required special consideration and monitoring for unanticipated side-effects.[20]

Nearly all the patients treated in the proton cohort in this study had tumour-directed surgery before proton therapy. The low general incidence of craniopharyngioma, and often acute presentation, explain why the first tumour-directed surgery was done at the referring institutions in some cases. This study using first-generation proton therapy showed contemporary trends in the surgical management of craniopharyngioma. Patients were treated with a variety of surgical approaches, including craniotomy, multiple surgical approaches, endoscopic resection, transnasal approaches, and open and closed Ommaya-catheter placements. Additional studies will be required to determine whether the type of surgical approach ultimately affects tumour control or functional outcome after irradiation. The trend towards using hypothalamus-sparing approaches is apparent in the series of Madsen and colleagues,[21] who showed that endonasal resection results in less injury to children and a higher rate of gross-total resection than surgery done using open procedures. The authors showed that rates of ischaemia were higher in patients treated using open procedures than closed procedures when matched for initial tumour size, and that BMI was uniformly higher in the open procedure group.

Considering that there is no difference in disease control when comparing patients treated with radical surgery to those treated with more limited surgery and irradiation,[3] we were selective when considering radical surgery and favoured the use of limited surgery and irradiation. Rock and colleagues[22] showed that more

than 30% of patients with craniopharyngioma have post-operative complications and 15% have major complications, defined as single or multiorgan dysfunction that would require intermediate care or management in an intensive care unit. Hypertension and duration of surgery were found to be risk factors when determining the incidence of severe complications. The incidence and severity of postoperative complications appear to be reduced in the modern treatment era. Fouda and colleagues[23] evaluated the effects of contemporary treatment approaches. They observed reductions in the incidence of visual complications, panhypopituitarism and diabetes insipidus, cognitive impairment, and obesitywith modern treatment approaches. Tan and colleagues[24] showed no change in overall rates of recurrence, hypothalamic obesity, hypothalamic damage, or vision loss when comparing patients treated before 2000 to those treated after 2000; however, they did find a lower incidence of diabetes insipidus and panhypopituitarism among patients treated with partial resection and limited surgery than in those treated with complete resection.

When dose reductions to healthy tissues were assessed by method, the extent of normal tissue sparing of proton therapy over advanced photon-based methods was found to depend on tumour location.[25] For patients with suprasellar tumours, proton therapy was more likely to be superior to photon therapy due to reducing exposure of the subventricular zones and hippocampi. Although the goal of clinicians is to eventually evaluate these patients for their long-term cognitive outcomes, addressing the issue of severe complications of proton therapy and preserving the prescribed dose of 54 CGE is of immediate importance. Indeed, the promise of proton therapy for suprasellar tumours largely relies on improved cognitive outcomes. In a study of children treated using proton therapy, those given focal irradiation, including young children and those with craniopharyngiomas, appeared to be spared substantial cognitive decline compared with patients treated with craniospinal irradiation; although the follow-up in this study was short.[26] Our findings are consistent with initial reports in the literature that suggest reduced risk for declines in intelligence[27,28] and adaptive functioning[29] following proton therapy. Our study has the advantage of a large, prospectively followed-up sample, with minimal attrition, and cognitive surveillance for 5 years, and a well-matched photon comparison group. Furthermore, mean radiation dose to the temporal lobes was related to decline in intellectual functioning regardless of modality, providing direct evidence that reduced dose to healthy tissues is driving at least some of the cognitive benefit of proton therapy.

Necrosis was observed in two patients in the proton cohort. Necrosis is an uncommon but expected complication of radiotherapy. In children with brain tumours treated with radiotherapy, the highest incidence is observed in those treated with high-dose craniospinal irradiation and boost treatment to posterior fossa subsites.[30] Radiation necrosis predominantly affects white matter and is thought to occur after small-artery injury and thrombotic occlusion. It results from increased tissue pressure from oedema and vascular injury leading to infarction, damage to endothelial cells, and fibrinoid necrosis of small arteries and arterioles.[31]

Vasculopathy is common among patients with craniopharyngioma and is responsible for some of the devastating effects observed after radiotherapy. The incidence, time to onset, and other factors predictive of severe and life-threatening vasculopathy have not been studied systematically.[32] Surgery is believed to be responsible for perioperative vasospasm and ischaemia, whereas late events are largely attributable to radiation dose and volume. Boekhoff and colleagues[33] reported an 11% incidence of cerebral ischaemia in patients with surgically treated craniopharyngioma. The showed in a multivariable analysis that hydrocephalus and gross-total resection were significant risk factors for cerebral ischaemia. Among 12 patients in their series treated with radiotherapy,[33] ischaemia was present before irradiation in all cases. Managing vasculopathy is often difficult because medical or surgical intervention is instituted or considered only after the process has become established. Our study shows that the cumulative incidence of vasculopathy is similar with proton and photon therapy; however, longer-term evaluation is required. In the meantime, clinicians seek new ways to identify risk factors for vasculopathy, improve imaging protocols to study vascular effects of irradiation, and streamline assessments for early intervention.

We found that 40 (43%) of 94 patients had visual impairment before irradiation. This value was similar or better than the proportion with visual impairment at diagnosis of craniopharyngioma reported by Wijnen and colleagues (74% of adults and 59% of children).[34] Although the proportion of patients with any level of visual impairment increased in our study, this value remained lower than the long-term proportion of patients with visual acuity (63%) and visual field (66%) impairment noted in by Wijnen[34] that combined patients who were treated with radiotherapy and those who were not. The effects of surgery on visual outcomes were studied by Akinduro and colleagues.[35] Their systematic review of adults treated with surgery showed that there was no difference in impaired or improved vision in patients treated with gross-total resection (GTR) versus those not treated with GTR. The rate of improved vision was 10% regardless of surgical extent and the rates of improved vision were 42% for GTR compared with 38% for those not treated with GTR. They concluded that GTR was not necessary to achieve meaningful decompression in patients with visual impairment at diagnosis.

Generally, there is a high incidence of hypopituitarism and diabetes insipidus in patients diagnosed and treated for craniopharyngioma. Although detailed information

about hypopituitarism and diabetes insipidus was available for both cohorts in our study, we did not include it as an endpoint in our study because of the substantial proportion of patients who present with pre-existing deficits before radiotherapy. Furthermore, diabetes insipidus is not considered a radiotherapy-induced side effect because the incidence is low or non-existent. Diabetes insipidus most often arises after surgery and might occasionally be present at the time of diagnosis.

Our study has several limitations. The use of a historic cohort is susceptible to the inherent differences encountered when performing and interpreting assessments, and external factors beyond the health-care environment, such as socioeconomic status.[36] Patients with craniopharyngioma were amongst a cohort of children and adolescents with localized brain tumors where SES was a predictor of cognitive performance. The relative additional costs of proton therapy, including equipment, staffing, and access, compared with photon therapy, are substantial, and affect the generalisability of our findings. Craniopharyngioma is a rare disease, and a randomised study would not be feasible. Both the proton study and photon study assessments were done under the supervision of the same follow-up team and were consistent across both studies.

We found no difference between proton therapy and photon therapy in terms of progression-free survival, or overall survival. Event-free survival (tumour progression and death from other cause events) was not reported since there were no deaths in the proton cohort. The potential benefit of proton therapy in the treatment of craniopharyngioma is to reduce the volume of healthy brain exposed to low doses. This is most relevant to crucial structures not adjacent to the targeted volume. A reduction in the volume of healthy brain exposed to radiation seems to reduce the cognitive effects of irradiation. Further improvements will require careful study, assessment of relevant domains, and long-term follow-up.

Contributors

TEM, RBK, NDS, YL, DJI, and HMC conceptualised the study. TEM, SW, YL, DJI, HMC, and EAB were responsible for data curation. TEM, SW, and YL did the formal analysis. TEM was responsible for funding acquisition. TEM, MEH, RBK, NDS, PK, FB, NJ, ESS, PRA, DJI, HMC, and EAB undertook the investigations. TEM, SW, and YL did the methodology. TEM was responsible for project administration. TEM, MEH, RBK, NDS, PK, FB, SW, YL, NJ, ESS, PRA, DJI, and HMC searched for resources. TEM, SW, and YL used the software for analysis. TEM, NJ, DJI, and HMC were responsible for supervision. TEM, SW, YL, NJ, and HMC validated the study. TEM, SW, YL, NJ, and HMC did the data visualisation. TEM and HMC wrote the initial draft, and TEM, MEH, RBK, NDS, PK, FB, SW, YL, NJ, ESS, PRA, DJI, and HMC wrote, reviewed, and edited the manuscript. TM, SW, HC, and YL accessed and verified the underlying study data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests

Data sharing

Participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices) will be available after publication (no end date) upon reasonable request to the corresponding author.

Acknowledgments

This study was funded by the American Lebanese Syrian Associated Charities, American Cancer Society, Cancer Center Support (CA21765-23) from the US National Cancer Institute, and Research to Prevent Blindness. We thank Christina Bosley, Annie Rini, Valerie Carr, Jorden Cunningham, Tina Davis, and Margaret Madey for their help and assistance with this research and to the nursing staff in the Department of Radiation Oncology, and psychological examiners in the Department of Psychology at St Jude Children's Research Hospital.

References

1 Muller HL, Merchant TE, Puget S, Martinez-Barbera JP. New outlook on the diagnosis, treatment and follow-up of childhood-onset craniopharyngioma. *Nat Rev Endocrinol* 2017; **13:** 299–312.

2 Muller HL. Childhood craniopharyngioma: current controversies on management in diagnostics, treatment and follow-up. *Expert Rev Neurother* 2010; **10:** 515–24.

3 Hill TK, Baine MJ, Verma V, et al. Patterns of care in pediatric craniopharyngioma: outcomes following definitive radiotherapy. *Anticancer Res* 2019; **39:** 803–07.

4 Maarouf M, El Majdoub F, Fuetsch M, et al. Stereotactic intracavitary brachytherapy with P-32 for cystic craniopharyngiomas in children. *Strahlenther Onkol* 2016; **192:** 157–65.

5 Suh JH, Gupta N. Role of radiation therapy and radiosurgery in the management of craniopharyngiomas. *Neurosurg Clin N Am* 2006; **17:** 143–48.

6 Boehling NS, Grosshans DR, Bluett JB, et al. Dosimetric comparison of three-dimensional conformal proton radiotherapy, intensity-modulated proton therapy, and intensity-modulated radiotherapy for treatment of pediatric craniopharyngiomas. *Int J Radiat Oncol Biol Phys* 2012; **82:** 643–52.

7 Edmonston DY, Wu S, Li Y, Khan RB, Boop FA, Merchant TE. Limited surgery and conformal photon radiation therapy for pediatric craniopharyngioma: long-term results from the RT1 protocol. *Neuro Oncol* 2022; **24:** 2200–09.

8 Merchant TE, Dangda S, Hoehn ME, et al. Pediatric craniopharyngioma: the effect of visual defincit and hormone deficiencies on long-term cognitive outcomss after conformal photon radiation therapy. *Int J Radiat Oncol Biol Phys* 2023; **115:** 581–91.

9 Merchant TE, Edmonston DY, Wu S, Li Y, Boop Fa, Lustig RH. Endocrine outcomes after limited surgery and conformal photon radiation therapy for pediatric craniopharyngioma: long-term results from the RT1 protocol. *Neuro Oncol* 2022; 24: 2210–20.

10 Wechsler D. Wechsler intelligence scale for children, fourth edition (WISC-IV). San Antonio, TX: Psychological Corporation, 2003.

11 Wechsler D. Wechsler adult intelligence scale, fourth edition (WAIS-IV). San Antonio, TX: Psychological Corporation, 2014.

12 Harrison P. Adaptive behavior assessment system, second edition (APAS-11). San Antonio, TX: Harcourt Assessments, 2003.

13 Wechsler D. Wechsler intelligence scale for children, third edition (WISC-III). San Antonio, TX: Psychological Corporation, 1991.

14 Wechsler D. Wechsler adult intelligence scale, third edition (WISC-III). San Antonio, TX: Psyschological Corporation, 1997.

15 Sparrow SBD, Cicchetti D. Vineland adaptive behavior scales. Circle Pines, MN: American Guidande Service, 1884.

16 Merchant TE. Clinical controversies: proton therapy for pediatric tumors. *Semin Radiat Oncol* 2013; **23:** 97–108.

17 Merchant TE, Kun LE, Hua CH, et al. Disease control after reduced volume conformal and intensity modulated radiation therapy for childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys* 2013; **85:** e187–92.

18 Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. *Int J Radiat Oncol Biol Phys* 2012; **82:** e281–87.

19 Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer* 2008; **51:** 110–17.

20 Paganetti H. Relating the proton relative biological effectiveness to tumor control and normal tissue complication probabilities assuming interpatient variability in alpha/beta. *Acta Oncol* 2017; **56:** 1379–86.

21 Madsen PJ, Buch VP, Douglas JE, et al. Endoscopic endonasal resection versus open surgery for pediatric craniopharyngioma: comparison of outcomes and complications. *J Neurosurg Pediatr* 2019; **1:** 1–10.

22 Rock AK, Dincer A, Carr MT, Opalak CF, Workman KG, Broaddus WC. Outcomes after craniotomy for resection of craniopharyngiomas in adults: analysis of the National Surgical Quality Improvement Program (NSQIP). *J Neurooncol* 2019; **144:** 117–25.

23 Fouda MA, Scott RM, Marcus KJ, et al. Sixty years single institutional experience with pediatric craniopharyngioma: between the past and the future. *Childs Nerv Syst* 2020; **36:** 291–96.

24 Tan TSE, Patel L, Gopal-Kothandapani JS, et al. The neuroendocrine sequelae of paediatric craniopharyngioma: a 40-year meta-data analysis of 185 cases from three UK centres. *Eur J Endocrinol* 2017; **176:** 359–69.

25 Adeberg S, Harrabi SB, Bougatf N, et al. Dosimetric comparison of proton radiation therapy, volumetric modulated arc therapy, and three-dimensional conformal radiotherapy based on intracranial tumor location. *Cancers* 2018; **10:** 11.

26 Pulsifer MB, Duncanson H, Grieco J, et al. Cognitive and adaptive outcomes after proton radiation for pediatric patients with brain tumors. *Int J Radiat Oncol Biol Phys* 2018; **102:** 391–98.

27 Kahalley LS, Ris MD, Grosshans DR, et al. Comparing intelligence quotient change after treatment With proton versus photon radiation therapy for pediatric brain tumors. *J Clin Oncol* 2016; **34:** 1043–49.

28 Kahalley LS, Peterson R, Ris MD, et al. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. *J Clin Oncol* 2020; **38:** 454–61.

29 Roth AK, Ris MD, Orobio J, et al. Cognitive mediators of adaptive functioning outcomes in survivors of pediatric brain tumors treated with proton radiotherapy. *Pediatr Blood Cancer* 2020; **67:** e28064.

30 Murphy ES, Merchant TE, Wu S, et al. Necrosis after craniospinal irradiation: results from a prospective series of children with central nervous system embryonal tumors. *Int J Radiat Oncol Biol Phys* 2012; **83:** e655–60.

31 Gilbert HA, Kagan AR. Radiation Damage to the Nervous System: a delayed therapeutic hazard. *J Comp Assist Tomography* 1981; **5:** 603.

32 Liu AK, Bagrosky B, Fenton LZ, et al. Vascular abnormalities in pediatric craniopharyngioma patients treated with radiation therapy. *Pediatr Blood Cancer* 2009; **52:** 227–30.

33 Boekhoff S, Bison B, Genzel D, et al. Cerebral infarction in childhood-onset craniopharyngioma patients: results of KRANIOPHARYNGEOM 2007. *Front Oncol* 2021; **11:** 698150.

34 Wijnen M, van den Heuvel-Eibrink MM, Janssen J, et al. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol* 2017; **176:** 755–67.

35 Akinduro OO, Izzo A, Lu VM, et al. Endocrine and visual outcomes following gross total resection and subtotal resection of adult craniopharyngioma: systematic review and meta-analysis. *World Neurosurg* 2019; **127:** e656–68.

36 Torres VA, Ashford JM, Wright E, et al. The impact of socioeconomic status (SES) on cognitive outcomes following radiotherapy for pediatric brain tumors: a prospective longitudinal trial. *Neurol Oncol* 2021; **23:** 1173–82.