Outcome after Modern Proton Beam Therapy in Childhood Craniopharyngioma; Results of the Prospective Registry Study KiProReg

M. Bischoff MD , D. Ahmad Khalil MD , S. Frisch PhD , CM. Bäcker PhD , S. Peters MD , C. Friedrich MD , S. Tippelt MD , R-D. Kortmann MD , B. Bison MD , HL. Müller MD , B. Timmermann MD

PII: S0360-3016(24)00432-2
DOI: https://doi.org/10.1016/j.ijrobp.2024.03.015
Reference: ROB 28771

To appear in: *International Journal of Radiation Oncology, Biology, Physics*

Received date: 12 October 2023
Revised date: 24 February 2024
Accepted date: 10 March 2024

Please cite this article as: M. Bischoff MD , D. Ahmad Khalil MD , S. Frisch PhD , CM. Bäcker PhD , S. Peters MD , C. Friedrich MD , S. Tippelt MD , R-D. Kortmann MD , B. Bison MD , HL. Müller MD , B. Timmermann MD , Outcome after Modern Proton Beam Therapy in Childhood Craniopharyngioma; Results of the Prospective Registry Study KiProReg, *International Journal of Radiation Oncology, Biology, Physics* (2024), doi: https://doi.org/10.1016/j.ijrobp.2024.03.015

Outcome after Modern Proton Beam Therapy in Childhood Craniopharyngioma; Results of the Prospective Registry Study KiProReg

Short running title: Modern proton beam therapy in childhood-onset craniopharyngioma

M. Bischoff, MD[1,2], D. Ahmad Khalil, MD[1], S. Frisch, PhD[1], CM. Bäcker, PhD[3], S. Peters, MD[1], C. Friedrich, MD[4], S. Tippelt, MD[5], R-D. Kortmann, MD[6], B. Bison, MD[7], HL. Müller, MD[4], B. Timmermann, MD[1,8]

[1]Department of Particle Therapy, University Hospital Essen, West German Proton Therapy Centre Essen (WPE), West German Cancer Centre (WTZ), 45147 Essen, Germany; [2]Department of Radiation Oncology, Ruhr-University Bochum, Medical Faculty, Marien Hospital, 44625 Herne, Germany; [3]West German Proton Therapy Centre Essen (WPE), West German Cancer Centre (WTZ), 45147 Essen, Germany; [4]Department of Paediatrics and Paediatric Haematology/Oncology, University Children's Hospital, Carl von Ossietzky University Oldenburg, Klinikum Oldenburg AöR, 26133 Oldenburg, Germany; [5]Department of Paediatrics III, Paediatric Oncology and Haematology, University Hospital Essen, 45147 Essen, Germany; [6]Department of Radiation Oncology, University of Leipzig, 04103 Leipzig, Germany; [7]Diagnostic and Interventional Neuroradiology, Faculty of Medicine, University of Augsburg, 86156 Augsburg, Germany; [8]German Cancer Consortium (DKTK), Germany

Corresponding author and responsible for statistical analysis:

Martin Bischoff, MD. Department of Particle Therapy, University Hospital Essen, West German Proton Therapy Centre Essen (WPE), West German Cancer Centre (WTZ), Hufelandstraße 55, 45147, Essen, Germany; Email: martin.bischoff@ruhr-uni-bochum.de

Conflict of Interest:

B.B. has received fees and hardware for her work at the Neuroradiological Reference Centre for the HIT-Studies supported by German Childhood Cancer Foundation (Deutsche Kinderkrebsstiftung). B.B. received lecture honorarium from Merck Healthcare Germany GmbH., H.L.M. has received reimbursement of participation fees for scientific meetings and continuing medical education events from following companies: Ferring, Lilly, Pfizer, Sandoz/Hexal, Novo Nordisk, IPSEN, and Merck Serono. H.L.M received reimbursement of travel expenses from IPSEN and Rhythm and lecture honoraria from Pfizer and Rhythm.

Funding: None.

Data Availability Statement:

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Acknowledgement:

We thank Christina Finke, Ulrike Naumann, and Ilka Nitschke (all West German Proton Therapy Centre Essen, Germany) for updating registry data.

Abstract

Background: Craniopharyngiomas (CPs) are rare tumours of the sellar region often leading to significant comorbidities due to their close proximity to critical structures. Aim of this study was to analyse survival outcome and late toxicities after surgery and proton beam therapy (PBT) in childhood CPs.

Patients and methods: Within the prospective XXXX study (XXXX), data of 74 childhood patients with CP, receiving PBT between 08/2013-06/2022 were eligible. Late toxicities were analysed according to the grading system of CTCAE 4.0.

Results: Median follow-up (FU) since first diagnosis was 4.3 years (range, 0.8-14.7). 75.7% of patients received PBT at time of disease progression or recurrence, whereas 24.3% as part of their primary therapy (definitive or adjuvant). Predominantly (85.1%), pencil beam scanning technique was used. Median total dose and initial tumour volume were 5400 cGyRBE (relative biological effectiveness) and 17.64 cm^3 (range, 3.07-300.59), respectively. The estimated (±SE) 3-year overall survival, progression-free and cystic failure-free survival rate after PBT were 98.2% (±1.7), 94.7% (±3.0), and 76.8% (±5.4), respectively. All local failures (n=3) were in-field relapses necessitating intervention and occurred exclusively in patients receiving PBT at progression or recurrence. Early cystic enlargements after PBT were typically asymptomatic and self-limiting. Fatigue, headaches, vision disorders, obesity and endocrinopathies were the predominant late toxicities. No high grade (≥3) new-onset visual impairment or cognitive deterioration occurred compared to baseline. The presence of cognitive impairments at the end of FU correlated with size of the planning target volume (p=0.034), D_{mean} dose to the temporal lobes (p=0.032,p=0.045) and the number of surgical interventions prior to PBT (p=0.029).

Conclusions: Our findings demonstrate favourable local control rates using modern PBT with acceptable late toxicities. Cyst growth within 12 month after radiotherapy is typically not associated with tumour progression. Longer FU has to be awaited to confirm results.

Keywords: Craniopharyngioma, proton beam therapy, radiotherapy, paediatrics, survival, outcome, sequelae

Introduction

Craniopharyngiomas (CPs) are benign intracranial neoplasms. Reported incidence rates range from 0.5 to $2.5/10^6$ population per year, with 30-50% occurring during childhood and

adolescence [1, 2]. Since the 5th Edition (2021) of the WHO classification of CNS tumours, CPs are divided into two distinct tumour types (adamantinomatous CPs and papillary CPs) given their different characteristics [3]. Adamantinomatous CP (ACP) represent the majority of CPs with onset during childhood [4]. The tumours are typically located in the sellar region and thereby in close proximity to sensitive critical organs, such as optic chiasm and neuroendocrine structures. ACP in particular tends to form cysts with sometimes extreme, space-occupying dimensions [5] leading to hormonal deficits, visual impairments and other physical limitations prior to treatment [6, 7].

Current treatment options include either complete resection or a limited surgical strategy followed by radiotherapy (RT), for example, if the hypothalamus is involved [8-10]. Disease progression, either cystic or nodular, may necessitate further interventions, which in turn may be associated with additional functional and qualitative limitations for the patient [11]. In addition to tumour control, preventing further morbidity and maintaining a high health-related quality of life (QoL) is of high priority.

While survival rates (OS and PFS) following GTR or STR + RT as an initial treatment concept are reported to be comparable in meta-analysis of multiple studies [12], the consistency of data regarding sequelae across studies [13-16] is lacking. In particular, the impact of the timing of RT administration on the occurrence of adverse events remains controversial [11, 17-19].

Especially in children, RT related long-term side effects are of concern. To minimize ionizing dose outside the target area, highly conformal techniques such as proton beam therapy (PBT) are increasingly used in paediatric patients with CP [8, 20]. PBT following surgery achieved promising results in terms of overall survival (OS) and progression free survival (PFS) [13, 17, 18, 21, 22]. Limited data is available that include larger patient cohorts treated with a modern PBT technique like active pencil beam scanning (PBS). So far, results of multidisciplinary

approaches, predominantly used passively scattered proton therapy [13, 17, 18, 21, 22]. Objective of this study was to report on survival outcome and late toxicities in a large single-institution cohort of childhood CP after surgery and PBT using primarily PBS.

Patients and Methods

Patients were eligible for this analysis if enrolled in the prospective XXXX study XXXX (XXXX). Informed consent of their legal guardian(s) was obtained at time of initial presentation at the treatment centre. Consent included treatment data assessment, analysis, and publication. Participation in the registry study was optional and did not influence the treatment concept. Data of 84 patients with CP (<18 years at time of RT) from the XXXX who received PBT between August 2013 and June 2022 was available for this analysis. Ethical approval (XXXX) was obtained from the local Ethics Committee. The inclusion criteria for the study were consent for enrolment in the registry and age <18 years. Patients were excluded in case of prior RT, combined photon/proton treatment or if FU data was not available (***Figure 1***). Eventually, data of 74 patients were analysed. Treatment concepts were performed according to XXXX (n=59) and XXXX (n=15), respectively.

Treatment-planning

Children were typically positioned in supine position and immobilised by a thermoplastic mask on a head frame. Planning softwares were RayStation up to version 10B (RaySearch Laboratories AB, SE-104 30 Stockholm, Sweden) and XIO (Elekta, Sweden), respectively. Target volume delineation was based on planning CT and pre- and post-surgery co-registered diagnostic MRI. Gross tumour volume (GTV) was defined as the residual tumour (solid and cystic tumour components demonstrated on MRI with contrast enhanced T1- and T2-weighted images) or the tumour bed after surgery. The clinical target volume (CTV) had a uniform margin of 0.5 cm but was manually corrected in the proximity of anatomical barriers

and was reduced to 0-0.3 cm when invasion was unlikely. Areas, expected to be at low risk for recurrence, such as regions with resected cyst walls or tumour bed of the primary tumour in late recurrences, were individually excluded from the CTV after discussion with study centre/ reference radiotherapy. Patients received PBT via either PBS, uniform scanning (US) or a combination of US/PBS. A few patients were treated with PBS plus static aperture. PBS treatment plans were robustly optimised on CTV with a density and setup uncertainty of 3.5% and 0.3 cm, respectively. US-plans were based on CTVs plus a uniform planning target volume (PTV)-margin of 0.3-0.5 cm, depending on expected cyst growth. The prescribed dose coverage of the PTV generally required that at least 95% of the volume should receive a dose of at least 5130 cGy (relative biological effectiveness [RBE]). The prescribed total dose was 5400 cGy (RBE) as D50 of PTV using conventional fractionation of 180 cGy (RBE) per day. According to the XXXX and XXXX treatment concepts, dose constraints were not specified. Dose prescription was based on the ICRU 50/62, and institutional constraints were applied and defined as follows. Volumetric constraints used for optic nerve and chiasm was at most 5500 cGy (RBE) at 0.01 cm^3. The average dose to the temporal lobe was at most 2000 cGy (RBE) and 2500 cGy (RBE) at 30.00% volume, and for the hippocampus at most 2000 cGy (RBE) and 3000 cGy (RBE) at 30.00% volume. The corresponding PBS treatment plans utilised two to three fields at gantry angles around 100° / 260° and slight couch rotations to avoid stopping at cavities. Intensity modulated proton therapy technique with moderate dose modulation was applied in order to achieve dose limitations. For patients treated with US, a treatment plan with 2 to 4 fields was created. Image-guided radiation therapy (IGRT) was performed using orthogonal kV-imaging in two planes. Verification MRIs were usually performed biweekly during treatment, or more often depending on cyst dynamics. For Organs-at-risk (OAR), doses D_{max} and D_{mean} of chiasm, nervi optici, pituitary, hypothalamus, brainstem, cochleae, temporal lobes, and hippocampi were calculated.

Assessments

Depending on the extent of resection gross total (GTR), subtotal (STR), or biopsy/cyst aspiration were defined. GTR corresponded to complete tumour removal if confirmed by neuroradiologic imaging (MRI). Any tumour removal that did not result in GTR was defined as STR. Biopsy or cyst aspiration alone was defined as surgical sampling/cyst aspiration without attempting tumour resection. Hypothalamic involvement (HI) before resection was assessed based on findings during the neuroradiological review process and graded according to Müller et al. [23]. The total number of cranial surgery appointments prior PBT was documented and included tumour resections as well as procedures due to hydrocephalus, cyst enlargement, reservoir implantation or shunt replacement. Late adverse events (AEs) related to PBT (90 days or more after completing PBT) were classified as new or deteriorated AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [24]. CTCAEs recorded during FU belonged to the following system organ classes: “Ear and labyrinth disorders”, “Eye disorders”, “Neoplasms benign, malignant and unspecified (incl. cysts and polyps)”, “vascular disorders”, “endocrine disorders” and “surgical and medical procedures”. General toxicity data refer to all grade 1-2 AEs that occurred in at least 10% of patients and all high grade (≥ 3) AEs at baseline and during FU. Visual field and visual acuity impairments were summarised under the term "vision disorders," and memory impairment and cognitive disturbance were summarised under the term "cognitive impairments" for statistical analysis. According to the XXXX registry questionnaires and face-to-face FU consultations with a radiation oncologist from our centre were conducted. If an in-person FU visit was not possible, appointments were done via phone. Additionally, letters from referring physicians were assessed, where follow-up care was carried out in parallel. FU questionnaires (modified according to NCI-PRO-CTCAE® ITEMS-GERMAN Item Library Version 1.0), were filled in by the parents or legal guardians of younger patients. If patients reached adulthood during FU, the questionnaire were filled in

by themselves. Noted toxicities within questionnaires were reviewed and quantified by radiation oncologist during the FU consultations. The questionnaire included specific questions regarding noticeable changes in cognitive perception or performance (e.g., orientation, attention, or concentration disturbances) and “memory impairment (retentiveness)“. However, neuropsychological assessments were not routinely collected according to the registry protocol. With the exception of imaging, all FU consultations and examinations were performed within three month after PBT and annually thereafter, or prematurely if relevant symptoms occurred. Regarding the neuroendocrine status, laboratory parameters and/or provocation tests were evaluated in addition to clinical course parameters. The obesity level was evaluated using the age- and gender-adjusted BMI-standard deviation scores (BMI-SDS) [25, 26]. Respective reference data were used for patients ≤ 18 [26] and > 18 years of age [27]. Ophthalmological examinations (visual field and visual acuity) were performed according to the standards of the referring hospital. These reports were retrospectively analysed regarding "eye diseases" according to CTCAE . In general, MRIs (before or after contrast media administration; T1- and T2-weighted, layer thickness ≤ 3 mm) were performed by the referring hospital within 3 months after PBT, every 3 to 6 months thereafter, and annually after 5 years. Images of patients treated within the XXXX trial and XXXX registry were sent to a neuroradiological reference centre for review. Patients were defined as lost to FU in case of unsuccessful attempts of inviting patients to their annual FU and of unfruitful attempts of receiving reports of referring oncologists, respectively, three times in a row, or in case of patients refusing to further participate in the registry.

Survival

Overall survival (OS), progression-free survival (PFS), local failure (LF) and cystic failure-free survival (CFFS) were calculated. Progressive disease (PD) has been defined in accordance with the recommendations of the Response Assessment in Paediatric Neuro-

Oncology (RAPNO) committee [28], as any solid tumour growth showing a ≥25% increase relative to the baseline, and any cyst enlargement that results in acute, new-onset or progressive functional impairment, or necessitates surgical intervention, occurring after 12 months from the completion of RT. In-field relapses are considered as LFs of RT. OS was defined as the time from PBT completion until the date of death due to any cause, or until the date of last FU used for censoring. PFS was defined as the time from PBT completion until the date of PD. LF rates were calculated from PBT completion until the date of PD. CFFS was defined as the time from PBT completion until the date of any cyst enlargement that did not represent the PD criteria. Without any event, death or the date of the last FU was used for censoring in PFS and CFFS, respectively.

Statistical-Analysis

Distribution and relationship of attributes were calculated and compared using cross tables and chi-square tests. Bivariate Pearson's correlation was performed on the continuous variables. To analyse the association between most frequently occurring late toxicities, the initial tumour size, target volumes (CTV, PTV), D_{mean} of OARs and age at RT, a threshold search was conducted to divide quantitative data into two classes of qualitative variables using the mean value (≤ mean or > mean). Used mean values are shown in tables. Survival rates were estimated (±SE) using the Kaplan-Meier method. The log-rank test was used to test for differences in Kaplan-Meier curves stratified by specific variables. All statistical analyses are exploratory, not confirmatory. *P* values are regarded noticeable ("significant") in case of $p \leq 0.05$ without adjustment for multiple testing. Statistical analysis was performed using IBM SPSS Statistics software, version 29 (IBM Corp., Armonk, NY, USA) and R statistic software version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and treatment characteristics

The median FU was 4.3 years (range, 0.8-14.7 years) since initial diagnosis and 2.8 years (range: 0.3-8.9 years) since PBT completion, respectively. 48.6% of the cohort had a FU longer than three years since PBT. Sixty-eight patients (91.9%) underwent surgical tumour resection before PBT. The median time between initial diagnosis and PBT was 3.29 months for patients treated at primary diagnosis and 16.23 months in case of progression/recurrence. One patient was diagnosed with an implantation metastasis in the left ventricle besides the primary disease at the time after initial operation. Primary tumour site and the metastasis received local PBT with 54 Gy at 1.8 Gy per day. The treatment time course of two patients was longer than 45 days, due to complications with implanted devices. All details regarding patients' characteristics and PBT are presented in ***Table 1***. Larger initial tumour size was associated with larger size of GTV, CTV and PTV ($p<0.001$) and higher D_{mean} values of the OARs nervi optici, cochleae, brainstem, temporal lobes and hippocampi ($p<0.001$; $p\leq0.005$; $p<0.001$; $p<0.001$; $p<0.001$). A large CTV and PTV was associated with higher D_{mean} values of the OARs nervi optici, cochleae, temporal lobes, hippocampi, brainstem and chiasm ($p\leq0.002$; $p<0.001$; $p<0.001$; $p<0.001$; $p<0.001$; $p<0.001$). There was no association between initial tumour size, CTV and PTV regarding the D_{mean} values of pituitary and hypothalamus. D_{max} and D_{mean} to the OAR are displayed in ***Table 2***.

Survival

The estimated 3- year OS was 98.2% (±1.7 SE). One patient died due to pre-existing tumour-associated comorbidities 16.36 month after completion of PBT. The estimated 3- year PFS rate was 94.7% (±3.0). We observed three tumour progressions, each characterised as local failure (in-field). Two of these were solid, manifesting at 7.8 and 17.0 months after completion of PBT. The remaining represented a cystic progression that occurred after 23.5

months following PBT. The patients were symptomatic and required surgical intervention. The local failures in the group of patients receiving PBT at primary treatment compared to those receiving PBT in progressive or recurrent disease are presented in ***Figure 2***. The estimated 3-year LF rate after completion of RT was 5.3 % (±3.0). In comparison, the LF rates were 0 % for patients who were irradiated at primary treatment and 7 % (±3.9) for those treated at progression, respectively. All three patients received PBT for progressive or recurrent disease. Transient, non-PD cyst enlargement was observed by diagnostic imaging in 18 patients (24.3%). All of them showed regression of cyst volume on subsequent MRI. The estimated 3- month, 1- and 3-year CFFS was 82.4% (±4.4), 79.7% (±4.7) and 76.8% (±5.4), respectively. Cyst growth occurred at a median of 2.6 months after the completion of PBT (range, 1.5-40.1). Late cyst enlargement (≥ 12 months) without acute, new-onset or progressive functional impairment, was observed in 3 cases (after 37.0, 38.8, and 40.1 months) and occurred exclusively in the group of patients who received PBT at the time of progressive or recurrent disease. No significant differences in CFFS with regard to sex, age at PBT, size of initial tumour, size of target volumes (CTV/PTV), resection status, number of surgical intervention appointments before PBT, implanted cyst reservoir or tumour progression were observed.

Adverse-events

Considering late AEs after PBT, only two new AEs ≥ grade 3 occurred during FU (***Table 3***). One patient with pre-existing seizures and mental vigilance disturbances after multiple surgeries developed progressive brainstem symptoms, which could not be clearly attributed to irradiation, and finally died 16 months after completion of PBT. Another patient was diagnosed with a new grade 4 AE in the field of psychiatric disorders and necessitated admission to a psychiatric hospital after expressing suicidal ideation, most probably caused by intra-family conflicts. No other onsets ≥ grade 3 AEs were reported with regard to cognitive

impairment, vision disorders or neuroendocrine deficits. Pre- and post-PBT conditions are presented in ***Table 3***. Following interdisciplinary therapy, 57% of patients experienced visual impairments, 32% fatigue, 28% headaches, and 20% cognitive impairments, respectively. Impact of timing of PBT, HI, size of initial tumour, size of target volumes, OAR D_{mean} values, extent of resection, number of surgical interventions prior to PBT or age at PBT was analysed. The occurrence of vision disorders since diagnosis (n=42) was associated with the timing of PBT (p=0.021), showing more deficits in the group of patients irradiated at progression/recurrence compared to those irradiated at first diagnosis. The onset or deterioration of cognitive impairment (n=15) after PBT was associated with the size of PTV (p=0.034), D_{mean} dose to the temporal lobes (right:p=0.032; left:p=0.045) and the number of surgical interventions prior to PBT (p=0.029), showing more deficits in patients with larger PTV, higher D_{mean} values and number of interventions (***Figure 3., A-D***). Due to the wide range of D_{mean} temporal lobe values in our cohort, a more detailed illustration of the distribution below and above the cut-off (***Figure 3A+B***) is shown in ***Figure 4***. Patients with D_{mean} temporal lobe values below the cut-off, received a median of 10.3 Gy (left) and 10.7 Gy (right). Patients with D_{mean} temporal lobe values above the cut-off, received a median of 16.7 Gy (left) and 17.1 Gy (right).

A complete endocrine FU was available in 70 patients. Endocrine deficits were already numerous at baseline and continued to increase during FU. The most common deficits, in descending order (percentage pre/post RT), were thyroid-stimulating hormone (TSH)-deficiency (84.3/90), adrenocorticotropic hormone (ACTH)-deficiency (80/85.7), growth-hormone-deficiency (64.3/82.9), diabetes insipidus (DI) (74.3/77.1) and follicle-stimulating hormone / luteinising hormone (LH/FSH)-deficiency (38.6/44.3). The gender-adjusted BMI-standard deviation score could be determined in a total of 67 patients. At last contact (baseline value in brackets), we observed a SDS BMI ≥ +2 in 41.8% (38.8%) and ≥ +3 in 10.4% (7.5%)

of the patients, respectively. In four patients (5.4%), cranial imaging suggested new vascular malformations described as being most likely cavernomas occurring at a median time of 27.3 months (19.29-45.47) after PBT. All four patients remained asymptomatic and did not undergo any intervention. During follow-up, no cerebrovascular events were documented.

Discussion

To our best knowledge, this evaluation is the largest single-centre cohort published so far on patients with childhood CP treated with PBT using predominantly PBS. Although, there is only limited PBT data available on large paediatric patient cohorts, our results confirm previously published findings using different PBT techniques regarding 3-year OS and PFS rates ranging from 94.1-100% and 91.7-96.8%, respectively [17, 18, 22]. When comparing survival with previous proton therapy cohorts, analysis-related characteristics must be taken into account. 94 patients with CP were treated with passively scattered proton therapy at St. Jude [22]. Their 3-year PFS rate (96.8%) is similar compared to ours. However, the comparison of survival rates impedes due to different index times and divergent classification of cystic failure as PD. Neither are our results directly comparable with those of Jimenez and colleagues [18]. In their study, 77 patients were analysed receiving PBT after surgery. Inhere, only the growth of solid tumour components was recorded and considered as LF. Cyst progression after completion of PBT was not reported. However, they used the same calculation since completion of PBT for their LF analysis as ours. The 3-year LF rate was about 5.1% [18]. Based on Bishop et al.'s [17] nodular progression-free survival rate as an indicator for PFS, their estimated 3-year rate was 91.7% after a median FU of 33 month. This calculation is conservative when considering that in their PBT cohort, three patients experienced cystic progression with the need for intervention after PBT. In comparison to our cohort, this might have been considered as PD if it had occurred more than 12 months post-

PBT. Our data seem within the range of previously published survival rates, but a comparison is difficult and has to be made with caution. We could demonstrate a high local tumour control rate at an early FU stage. Trends beyond three years after PBT cannot be validly derived from our short FU and the associated low number at risk.

Criteria used to determine increased cystic components of a CP as progression is often inconsistent among publications. Merchant and colleagues [22] defined tumour progression as an increase of ≥ 25% in at least two consecutive imaging evaluations, beginning 2-3 years after treatment. The RAPNO working group does not consider an intervention-requiring increase in cystic tumour component within 12 months after RT as PD, but any cystic changes associated with new or worsening symptoms thereafter [28]. However, in our cohort, approximately a quarter (25.7%) of patients experienced an increase in cystic components during follow-up after PBT. Following the RAPNO recommendation, there was one case classified as PD. 18 out of 19 cyst enlargements regressed after a short period. Cyst enlargements did not result in noticeable functional impairments in our cohort. The median time to the occurrence of cyst enlargement was 2.6 months, which corresponds to the time of the first post-RT follow-up MRI. Late cyst enlargements in our cohort, either transient or as PD, occurred between 23.5 and 40.1 months. We can confirm that early cyst enlargement after RT is common, but typically asymptomatic. We do not observe any association between early cyst growth and recurrent cyst enlargement nor future cystic tumour progression. Our data indicate that an intervention-requiring cyst progression is relatively rare.

Our cohort had limited diversity in terms of their resection status, as the majority of patients (83.8%) received STR+PBT. However, there were no differences in outcome compared to the small number of patients who underwent GTR+PBT or biopsy/cyst puncture plus PBT. Comparative studies had shown that a conservative surgical approach followed by RT had significantly better recurrence rates than partial resections alone and similar control rates

compared with GTR alone [14, 29, 30]. Regardless, the focus of an optimal treatment strategy for children with a benign but quasi chronic disease, cannot rely on PFS alone. Instead, focus has to lay on QoL and reducing treatment-related morbidity. Fouda et al. [14] concluded that irradiation-induced morbidities and aggressive surgery-related morbidities after GTR were balanced, comparing outcomes between STR+RT and GTR based on their retrospective study over 60 years. Certainly, the hypothalamus is often in the range of high radiation doses as we could demonstrate. However, Elowe-Gruau et al. [15] showed that a hypothalamus-sparing strategy with surgical intervention followed by radiation resulted in better long-term outcomes regarding obesity and QoL compared to GTR alone. Besides, technical developments also need to be taken into account. Compared to Jimenez et al. [18] and Merchant et al. [22], who mainly (99% and 100%) used passive scattered PBT, our cohort with primarily PBS technique (85.1%) showed similar results regarding rates of toxicities.

For future patient treatments, multiple developments in optimised treatment planning will be introduced in clinical workflows. A few patients of our cohort were treated with PBS plus static aperture. The use of static apertures in PBS further improving field conformality has already been demonstrated at our centre [31, 32]. With the introduction of apertures to PBS, the lateral penumbra of the dose distribution has been reduced leading to less dose delivered to organs at risk lateral of the treatment fields [31, 32]. Compared to passive techniques, PBS allows to achieve lower dose delivered to temporal lobe or hippocampi as well as reduced integral whole brain dose. Furthermore, the opportunity of fluence modulations (intensity modulated proton therapy) allows for dose reduction close to the chiasm or optic nerve. Optimising the positioning of single pencil beam spots can further improve those effects [33, 34].

Several dosimetric comparison studies between conformal RT and different PBT approaches demonstrated the capabilities of PBT due to the characteristic rise and sharp fall off of the low

dose curve, commonly known as the Bragg peak [35-38]. With increasing use of better diagnostic information and high precision radiation techniques, smaller target volume margins were introduced [39]. Regarding PBT, margins used for CTV planning are still heterogeneous and range from 0.3-1 cm [13, 18]. The recently published study by Edmonston et al. [40], observing 101 childhood CP patients after photon-based conformal radiotherapy (CRT), found a significant association of larger PTV and increased risk of vasculopathy, after a median FU time of 14.9 years. Despite our comparatively early results regarding FU time, we found that cognitive impairments were more likely over time in patients with larger PTVs. Even if target volumes will highly depend on tumour volumes, we can conclude that restricting dose will have a benefit to reducing toxicity. This highlights the need for conformal RT techniques such as PBT. PBT has the advantage of reducing dose to non-involved healthy tissue, especially in the mid- and low-dose ranges. We could also demonstrate a correlation of the initial tumour size and the resulting CTV and PTV with respect to the D_{mean} of certain OARs. However, we found no association between both volumes and D_{mean} of pituitary and hypothalamus from which one can assume that sparing of OAR too close or even included into the target cannot be spared even when using PBT. This supports previous analyses of tumours in the skull base region, as conducted by Florijn et al. [41], comparing different radiation techniques (IMPT, IMRT, VMAT) with conventional and stereotactic dose prescription finding only small differences in the high dose region.

Regarding sequelae, visual impairment and neuroendocrine deficits are most commonly observed in this tumour entity [16, 42-44]. In our cohort, only two high grade (≥3) late toxicities were observed and no new-onset or deterioration of ≥ grade 3 visual or cognitive impairment occurred during FU. Within our cohort, almost all patients presenting with an elevated or pathological SDS BMI, at last contact, were already affected by obesity at baseline. This was within the expected range and is consistent with previous reports [45-47]. Our data confirmed

that CP-associated morbidities such as visual disorders, endocrine deficits or obesity are frequently observed prior to the initiation of RT.

However, a crucial aspect for the utilization of PBT in suprasellar tumours is grounded in the preservation of cognitive capacities due to dose-response relationships regarding the temporal lobes, especially the hippocampi. Recently, Merchant and colleagues [22] presented the impressive results of their prospective phase II trial, showing a decrement in intelligence quotient by 1.09 points/year and a decline in adaptive behaviour by 1.48 points/year when photon therapy was used compared to PBT. In contrast to their historical data post CRT, PBT managed to reduce the mean doses to the temporal lobes by approximately 10 Gy. Our analysis illustrates the expected dose-dependent increase in cognitive deficits after PBT. We observed a significant difference in cognitive impairments between the individual D_{mean} for the temporal lobes above and below the cut-off. D_{mean} temporal lobe values around 10.3 Gy (left) and 10.7 Gy (right) resulted in significant fewer cognitive deficits during FU compared to values around 16.7 Gy (left) and 17.1 Gy (right). These findings suggest a substantial impact of the temporal lobe D_{mean} on cognitive function and are in line with previous results of Merchant et al.[22].

However, the used CTCAE scores for cognitive outcome are non-specific and do not measure IQ alone, but can be used as general indicators for cognitive impairments. Tumour location and size are known to play an important role in dose distribution of OARs. We could demonstrate a correlation of PTV size and dose to the temporal lobes. Further, our results suggest that the tumour-dependent PTV size also allows conclusions to be drawn about the occurrence of neurocognitive deficits within the FU. Besides, data from our cohort indicates that more surgical procedures lead to an increased risk of cognitive impairments, supporting earlier findings by Alapetite and colleagues [48]. They showed retrospectively that more frequent short-term memory impairment and school difficulties arise upon irradiation after

multiple surgical procedures. In an earlier publication, Merchant and colleagues were able to demonstrate that, in addition to higher doses to the temporal lobes, a younger age at RT resulted in poorer developmental IQs, whereas early growth hormone substitution led to improved intelligence and attention outcomes [49]. In concordance with our data, it can be concluded that the development of cognitive abilities in patients with CPs is multifactorial due to tumour, host, and treatment factors. Keeping previous published results in mind, those investigations could help interpret and explain our findings on cognitive decline. However, we have to note that our evaluation does not allow a differentiated statement on cognitive performance, as no specific neuropsychological assessments were performed. Our analysis of tumour sizes, the number of surgical procedures and the dose to the temporal lobes suggests potential factors that may contribute to poorer neurocognitive outcome. These findings have to be interpreted with caution until supported by more sensitive assessments. Although the interpretation of CTCAE is comparatively less sensitive, it offers the possibility of comparing patients within larger cohorts. This way trends can be recognised and new insights gained from which hypotheses for future research can be derived.

Regarding quality of life and the development of treatment sequelae, timing of RT, directly adjuvant or in case of recurrence or progression is still controversial and may have an impact on treatment-related morbidity [11, 17-19]. Our findings suggest that PBT at the time of diagnosis is associated with fewer intervention-requiring progressions, which occurred exclusively in the group of patients receiving PBT in case of recurrence or progression. All 18 patients who underwent irradiation at first diagnosis (definite or adjuvant) remained free of intervention-requiring progression. Given the small number of progressions and the fact that about a quarter of our cohort received early PBT, these results have to be interpreted with caution. To draw conclusions regarding differences in subjectively perceived QoL depending on the timing of RT, patients in the German KRANIOPHARYNGEOM 2007 trial were

randomised after incomplete tumour resection to immediate postoperative RT vs. RT upon progression. The randomisation was stopped for futility in 2016 and only minor differences in terms of QoL were observed between the two treatment approaches [19]. Regarding QoL after incomplete resection (n=41) they stated that RT predominantly (65.9%) administered due to progression of residual tumours, was associated with reduced QoL. However, our findings are in contrast with previous reports by Jimenez et al. [18] who demonstrated no association between timing of RT and local failure and OS. Moon et al. [11] compared early (within 3 month) versus late (progression/relapse) RT delivery time regarding survival and QoL. With a median follow-up of 130 months, they stated that worse QoL in later irradiated patients were caused by repeated surgical interventions necessary due to the recurrence before RT treatment rather than due to the irradiation itself. Bishop et al. [17] demonstrated that patients who received irradiation as salvage therapy (for recurrence) rather than adjuvant therapy had higher rates of visual and endocrine impairment (P=0.017 and 0.024, respectively) which is consistent with our results, observing fewer vision disorders in the primary/adjuvant irradiated group. Our findings are in line with data that propose a potential benefit of early adjuvant radiotherapy avoiding repetitive surgeries. However, timing of radiation and extent of resection need to be individually evaluated over the course of disease within a MDT with regard to potential treatment toxicity versus an increased risk for recurrence.

We have to acknowledge several limitations of our study. Although the data was collected within a standardised, prospective registry study since 2013, some additional data were recorded retrospectively for this analysis (endocrinopathies, visual outcome, PD according to RAPNO). Our data represent early results with a relatively short FU period, suggesting trends, which need to be confirmed by a longer observation interval. Furthermore, patients from several national and international institutions were included, resulting in

heterogeneous examination standards and intervals during FU. In addition, standardised neurocognitive examinations were not part of the registry's regular programme.

Conclusion

Outcomes of children with CP after surgery and PBT showed excellent local tumour control rates. Early cyst enlargement after RT is common, although typically asymptomatic. We observe no direct correlation between early cyst growth and later progression within FU. Based on our data, it appears that cyst progression requiring intervention is rather a rare phenomenon after PBT, considering the frequent occurrences of cyst enlargement. Benefits of PBT could be further strengthened by the utilisation of recent technical developments in order to further reduce unnecessary dose to normal tissue. However, children after diagnosis and therapy of CP regularly present typical long-term morbidities. Regarding the significant relevance of endocrinopathies and anthropometric development in paediatric patients with CP, we have made the decision to conduct a dedicated analysis of the substantial data volume to explore this topic comprehensively. Further research in prospective trials is necessary, especially regarding the assessment of QoL and neurocognitive functions, but also optimal sequencing of treatment modalities. Longer FU has to be awaited to evaluate the full scope of late effects including cerebrovascular events and secondary malignancies.

References

1. Müller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera JP, Puget S. Craniopharyngioma. *Nat Rev Dis Primers*. 2019 Nov 7;5(1):75. doi: 10.1038/s41572-019-0125-9
2. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. *J Neurosurg*. 1998 Oct;89(4):547-51. doi: 10.3171/jns.1998.89.4.0547
3. Santagata S, Komori T, Müller HL, Pietsch T Adamantinomatous craniopharyngioma (Tumours of the sellar region). In: Brat DJ GA WP, ed. WHO Classification of Tumours Editorial Board Central nervous system tumours. WHO classification of tumours series. Vol 6. *5th Edition ed. Lyon (France): International Agency for Research on Cancer*; 2021:393-396
4. Momin AA, Recinos MA, Cioffi G, Patil N, Soni P, Almeida JP, Kruchko C, Barnholtz-Sloan JS, Recinos PF, Kshettry VR. Descriptive epidemiology of craniopharyngiomas in the United States. *Pituitary*. 2021 Aug;24(4):517-522. doi: 10.1007/s11102-021-01127-6
5. Sartoretti-Schefer S, Wichmann W, Aguzzi A, Valavanis A. MR differentiation of adamantinous and squamous-papillary craniopharyngiomas. *Am J Neuroradiol*. 1997 Jan;18(1):77-87
6. Müller HL. Childhood craniopharyngioma--current concepts in diagnosis, therapy and follow-up. *Nat Rev Endocrinol*. 2010 Nov;6(11):609-18. doi: 10.1038/nrendo.2010.168
7. Hoffmann A, Boekhoff S, Gebhardt U, Sterkenburg AS, Daubenbüchel AM, Eveslage M, Müller HL. History before diagnosis in childhood craniopharyngioma: associations

with initial presentation and long-term prognosis. *Eur J Endocrinol.* 2015 Dec;173(6):853-62. doi: 10.1530/EJE-15-0709

8. Marcus HJ, Rasul FT, Hussein Z, Baldeweg SE, Spoudeas HA, Hayward R, Jeelani NUO, Thompson D, Grieve JP, Dorward NL, Aquilina K. Craniopharyngioma in children: trends from a third consecutive single-center cohort study. *J Neurosurg Pediatr.* 2019 Dec 20:1-9. doi: 10.3171/2019.10.PEDS19147

9. Hussein Z, Glynn N, Martin N, Alkrekshi A, Mendoza N, Nair R, McCullough K, Marcus HJ, Dorward N, Grieve J, Fersht N, Dyson E, Bouloux PM, Druce M, Baldeweg SE. Temporal trends in craniopharyngioma management and long-term endocrine outcomes: A multicentre cross-sectional study. *Clin Endocrinol (Oxf).* 2021 Feb;94(2):242-249. doi: 10.1111/cen.14334

10. Müller HL. Risk-adapted, long-term management in childhood-onset craniopharyngioma. *Pituitary.* 2017 Apr;20(2):267-281. doi: 10.1007/s11102-016-0751-0

11. Moon SH, Kim IH, Park SW, Kim I, Hong S, Park CI, Wang KC, Cho BK. Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas--a study in single institute. *Childs Nerv Syst.* 2005 Aug;21(8-9):799-807. doi: 10.1007/s00381-005-1189-2

12. Wang G, Zhang X, Feng M, Guo F. Comparing survival outcomes of gross total resection and subtotal resection with radiotherapy for craniopharyngioma: a meta-analysis. *J Surg Res.* 2018 Jun;226:131-139. doi: 10.1016/j.jss.2018.01.029

13. Ravindra VM, Okcu MF, Ruggieri L, Frank TS, Paulino AC, McGovern SL, Horne VE, Dauser RC, Whitehead WE, Aldave G. Comparison of multimodal surgical and radiation treatment methods for pediatric craniopharyngioma: long-term analysis of progression-free survival and morbidity. *J Neurosurg Pediatr.* 2021 May 28:1-8. doi: 10.3171/2020.11.PEDS20803

14. Fouda MA, Scott RM, Marcus KJ, Ullrich N, Manley PE, Kieran MW, Goumnerova LC. Sixty years single institutional experience with pediatric craniopharyngioma: between the past and the future. *Childs Nerv Syst.* 2020 Feb;36(2):291-296. doi: 10.1007/s00381-019-04294-x

15. Elowe-Gruau E, Beltrand J, Brauner R, Pinto G, Samara-Boustani D, Thalassinos C, Busiah K, Laborde K, Boddaert N, Zerah M, Alapetite C, Grill J, Touraine P, Sainte-Rose C, Polak M, Puget S. Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. *J Clin Endocrinol Metab.* 2013 Jun;98(6):2376-82. doi: 10.1210/jc.2012-3928

16. Wijnen M, van den Heuvel-Eibrink MM, Janssen JAMJL, Catsman-Berrevoets CE, Michiels EMC, van Veelen-Vincent MC, Dallenga AHG, van den Berge JH, van Rij CM, van der Lely AJ, Neggers SJCMM. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol.* 2017 Jun;176(6):755-767. doi: 10.1530/EJE-17-0044

17. Bishop AJ, Greenfield B, Mahajan A, Paulino AC, Okcu MF, Allen PK, Chintagumpala M, Kahalley LS, McAleer MF, McGovern SL, Whitehead WE, Grosshans DR. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. *Int J Radiat Oncol Biol Phys.* 2014 Oct 1;90(2):354-61. doi: 10.1016/j.ijrobp.2014.05.051

18. Jimenez RB, Ahmed S, Johnson A, Thomas H, Depauw N, Horick N, Tansky J, Evans CL, Pulsifer M, Ebb D, Butler WE, Fullerton B, Tarbell NJ, Yock TI, MacDonald SM. Proton Radiation Therapy for Pediatric Craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2021 Aug 1;110(5):1480-1487. doi: 10.1016/j.ijrobp.2021.02.045

19. Eveslage M, Calaminus G, Warmuth-Metz M, Kortmann RD, Pohl F, Timmermann B, Schuhmann MU, Flitsch J, Faldum A, Müller HL. The Postoperative Quality of Life

in Children and Adolescents with Craniopharyngioma. *Dtsch Arztebl Int.* 2019 May 3;116(18):321-328. doi: 10.3238/arztebl.2019.0321

20. Friedrich C, Boekhoff S, Bischoff M, Beckhaus J, Sowithayasakul P, Calaminus G, Eveslage M, Valentini C, Bison B, Harrabi SB, Krause M, Timmermann B, Müller HL. Outcome after proton beam therapy versus photon-based radiation therapy in childhood-onset craniopharyngioma patients-results of KRANIOPHARYNGEOM 2007. *Front Oncol.* 2023 Oct 27;13:1180993. doi: 10.3389/fonc.2023.1180993

21. Alapetite C, Puget S, Nauraye C, Beccaria K, Bolle S, Lesueur P, Brisse H, Boddaert N, Dendale R, Doz F, Sainte-Rose C, Bouffet E, Habrand JL, CRAN-29. Conservative Surgery Followed by Proton Therapy for Craniopharyngioma in Children: A Phase II Study to Examine the Feasibility of Dose Escalation [Abstract], *Neuro Oncol.* 2018;20 (Suppl 2):i42–i43, https://doi.org/10.1093/neuonc/noy059.065

22. Merchant TE, Hoehn ME, Khan RB, Sabin ND, Klimo P, Boop FA, Wu S, Li Y, Burghen EA, Jurbergs N, Sandler ES, Aldana PR, Indelicato DJ, Conklin HM. Proton therapy and limited surgery for paediatric and adolescent patients with craniopharyngioma (RT2CR): a single-arm, phase 2 study. *Lancet Oncol.* 2023 May;24(5):523-534. doi: 10.1016/S1470-2045(23)00146-8

23. Müller HL, Gebhardt U, Teske C, Faldum A, Zwiener I, Warmuth-Metz M, Pietsch T, Pohl F, Sörensen N, Calaminus G; Study Committee of KRANIOPHARYNGEOM 2000. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *Eur J Endocrinol.* 2011 Jul;165(1):17-24. doi: 10.1530/EJE-11-0158

24. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf. Accessed January 10, 2024

25. Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr*. 1990 Jan;44(1):45-60

26. XXXX

27. XXXX

28. Hoffman LM, Jaimes C, Mankad K, Mirsky DM, Tamrazi B, Tinkle CL, Kline C, Ramasubramanian A, Malbari F, Mangum R, Lindsay H, Horne V, Daniels DJ, Keole S, Grosshans DR, Young Poussaint T, Packer R, Cavalheiro S, Bison B, Hankinson TC, Müller HL, Bartels U, Warren KE, Chintagumpala M. Response assessment in pediatric craniopharyngioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) Working Group. *Neuro Oncol.* 2023 Feb 14;25(2):224-233. doi: 10.1093/neuonc/noac221

29. Lin LL, El Naqa I, Leonard JR, Park TS, Hollander AS, Michalski JM, Mansur DB. Long-term outcome in children treated for craniopharyngioma with and without radiotherapy. *J Neurosurg Pediatr*. 2008 Feb;1(2):126-30. doi: 10.3171/PED/2008/1/2/126

30. Poiset, S. J., Ali, A., Cappelli, L., Shah, Y. B., Zhan, T., Evans, J., & Shi, W. Long-Term Outcome of Surgery and Radiation Treatment for Craniopharyngioma [Abstract]. *Int J Radiat Oncol Biol Phys*, 2022 Nov;114(Suppl 3):e47. https://doi.org/10.1016/j.ijrobp.2022.07.777

31. XXXX

32. XXXX

33. Winterhalter C, Lomax A, Oxley D, Weber DC, Safai S. A study of lateral fall-off (penumbra) optimisation for pencil beam scanning (PBS) proton therapy. *Phys Med Biol.* 2018 Jan 11;63(2):025022. doi: 10.1088/1361-6560/aaa2ad

34. XXXX

35. Boehling NS, Grosshans DR, Bluett JB, Palmer MT, Song X, Amos RA, Sahoo N, Meyer JJ, Mahajan A, Woo SY. 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 Feb 1;82(2):643-52. doi: 10.1016/j.ijrobp.2010.11.027

36. Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2012 Feb 1;82(2):e281-7. doi: 10.1016/j.ijrobp.2011.01.005

37. Armoogum KS, Thorp N. Dosimetric Comparison and Potential for Improved Clinical Outcomes of Paediatric CNS Patients Treated with Protons or IMRT. *Cancers (Basel).* 2015 Apr 28;7(2):706-22. doi: 10.3390/cancers7020706

38. Adeberg S, Harrabi SB, Bougatf N, Verma V, Windisch P, Bernhardt D, Combs SE, Herfarth K, Debus J, Rieken S. Dosimetric Comparison of Proton Radiation Therapy, Volumetric Modulated Arc Therapy, and Three-Dimensional Conformal Radiotherapy Based on Intracranial Tumor Location. *Cancers (Basel).* 2018 Oct 26;10(11):401. doi: 10.3390/cancers10110401

39. Merchant TE, Kun LE, Hua CH, Wu S, Xiong X, Sanford RA, Boop FA. Disease control after reduced volume conformal and intensity modulated radiation therapy for childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2013 Mar 15;85(4):e187-92. doi: 10.1016/j.ijrobp.2012.10.030

40. 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 Dec 1;24(12):2200-2209. doi: 10.1093/neuonc/noac124

41. Florijn MA, Sharfo AWM, Wiggenraad RGJ, van Santvoort JPC, Petoukhova AL, Hoogeman MS, Mast ME, Dirkx MLP. Lower doses to hippocampi and other brain structures for skull-base meningiomas with intensity modulated proton therapy compared to photon therapy. *Radiother Oncol.* 2020 Jan;142:147-153. doi: 10.1016/j.radonc.2019.08.019

42. Yaxian D, Chunmei Y, Juanyu X, Lei W, Jian G, Chengsong Z. An analysis of clinical characteristics and postoperative complications in children craniopharyngioma. *Childs Nerv Syst.* 2021 Oct;37(10):3033-3040. doi: 10.1007/s00381-021-05277-7

43. Greenfield BJ, Okcu MF, Baxter PA, Chintagumpala M, Teh BS, Dauser RC, Su J, Desai SS, Paulino AC. Long-term disease control and toxicity outcomes following surgery and intensity modulated radiation therapy (IMRT) in pediatric craniopharyngioma. *Radiother Oncol.* 2015 Feb;114(2):224-9. doi: 10.1016/j.radonc.2014.11.035

44. 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 Dec 1;24(12):2210-2220. doi: 10.1093/neuonc/noac115

45. Müller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R, Sörensen N. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3298-305. doi: 10.1210/jc.2003-031751

46. Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbüchel AM, Müller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro Oncol.* 2015 Jul;17(7):1029-38. doi: 10.1093/neuonc/nov044

47. Beckhaus J, Friedrich C, Boekhoff S, Calaminus G, Bison B, Eveslage M, Timmermann B, Flitsch J, Müller HL. Outcome after pediatric craniopharyngioma: the role of age at diagnosis and hypothalamic damage. *Eur J Endocrinol.* 2023 Mar 2;188(3):lvad027. doi: 10.1093/ejendo/lvad027

48. Alapetite C, Puget S, Ruffier A, Habrand JL, Bolle S, Noel G, Nauraye C, De Marzy L, Boddaert N, Brisse H, Sainte-Rose C, Zerah M, Boetto S, Laffond C, Chevignard M, Grill J, Doz F. CR-09. Proton therapy for craniopharyngioma in children: Update of the Orsay Proton Center experience [Abstract]. *Neuro Oncol.* 2012;14(Suppl 1): i22–i25. https://doi.org/10.1093/neuonc/nos097

49. Merchant TE, Dangda S, Hoehn ME, Wu S, Li Y, Wang F, Pan H, Boop FA, Jurbergs N, Conklin HM. Pediatric Craniopharyngioma: The Effect of Visual Deficits and Hormone Deficiencies on Long-Term Cognitive Outcomes After Conformal Photon Radiation Therapy. *Int J Radiat Oncol Biol Phys.* 2023 Mar 1;115(3):581-591. doi: 10.1016/j.ijrobp.2022.09.061

Figure Legends:

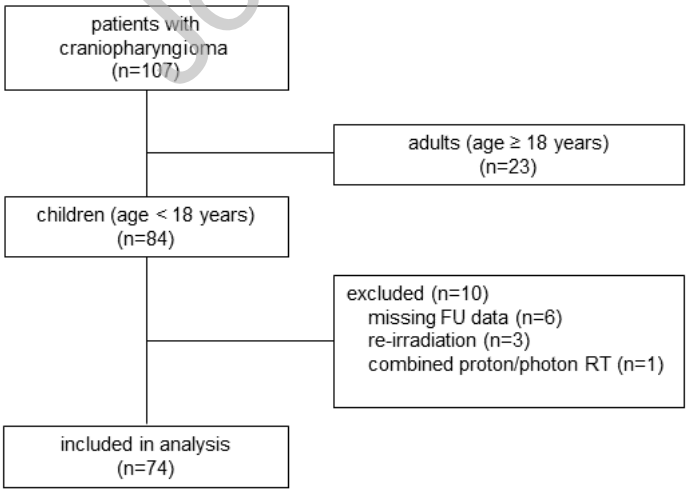

Figure 1. Flowchart; Presentation of the inclusion and exclusion criteria of the conducted analysis, including the associated patient numbers. Abbreviation: FU, follow-up; RT, radiotherapy

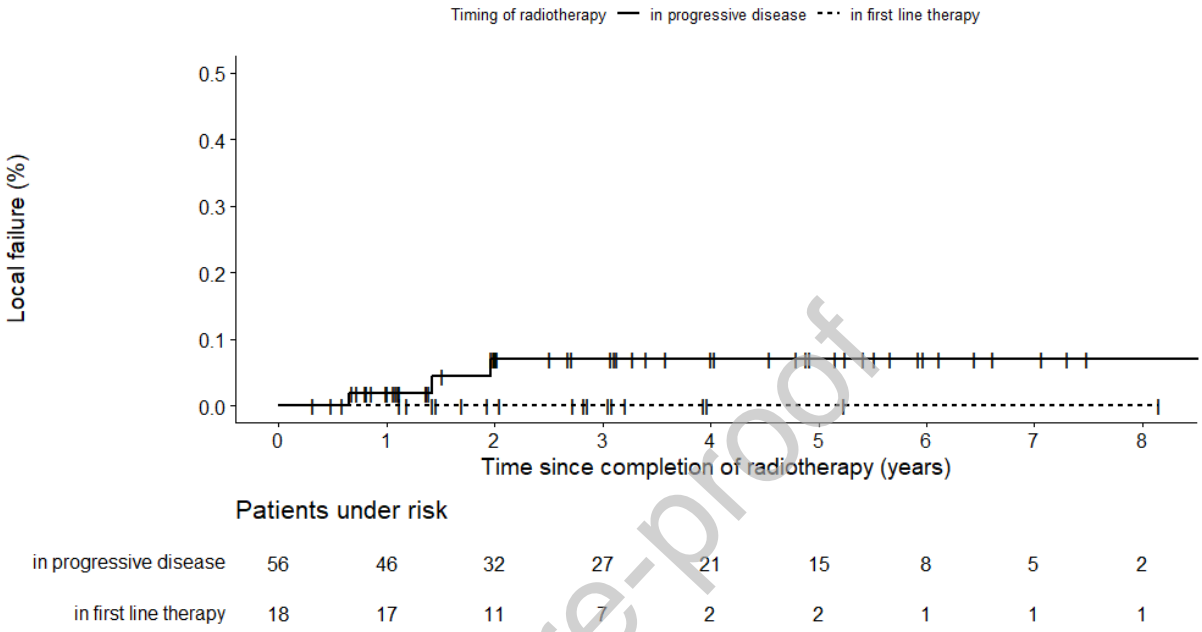

Figure 2. Local failure after RT; Local failure rates since completion of RT, comparing radiation time points at first event or at relapse/progression showing estimated 3-year rates of 0% and 7% (±3.9), respectively.

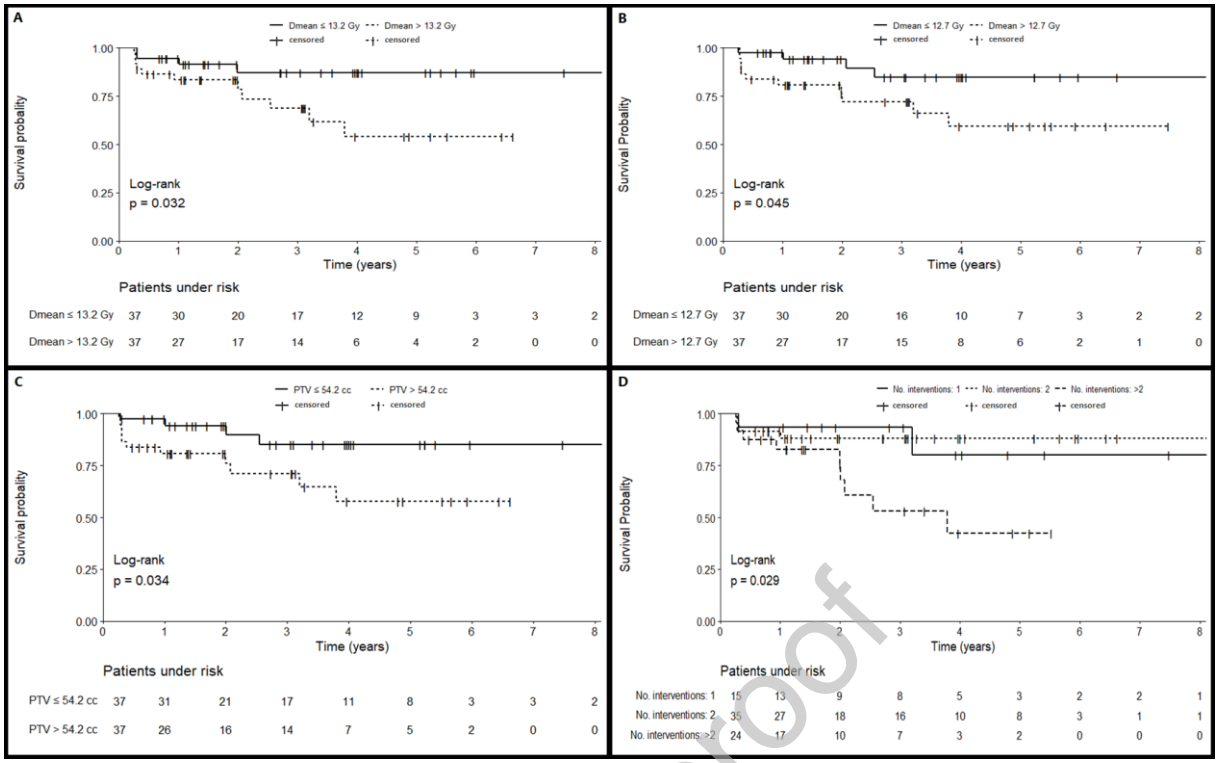

Figure 3. Cognitive deficit-free survival rates; Onset or deterioration of cognitive impairment after PBT in years, depending on various treatment modalities as risk factors: D_{mean} dose to the temporal lobes [right lobe: (A); left lobe: (B)], the size of PTV (C), and the number of surgical interventions prior to PBT (D). In 15 patients cognitive impairments were reported and classified as grade 1 or 2 according to CTCAE v. 4. D_{mean} doses and PTVs represent the 50th percentiles for the calculated mean doses / mean volume of the cohort: D_{mean} right temporal lobe (≤ 13.2 Gy or > 13.2 Gy) and D_{mean} left temporal lobe (≤ 12.7 Gy or > 12.7 Gy); mean PTV (≤ 54.2 cc or > 54.2cc). The number of surgical interventions prior to PBT was divided into three groups: only one intervention, two interventions, or more than two interventions. Abbreviations: D_{mean}, mean dose; PTV, planning target volume; No., number

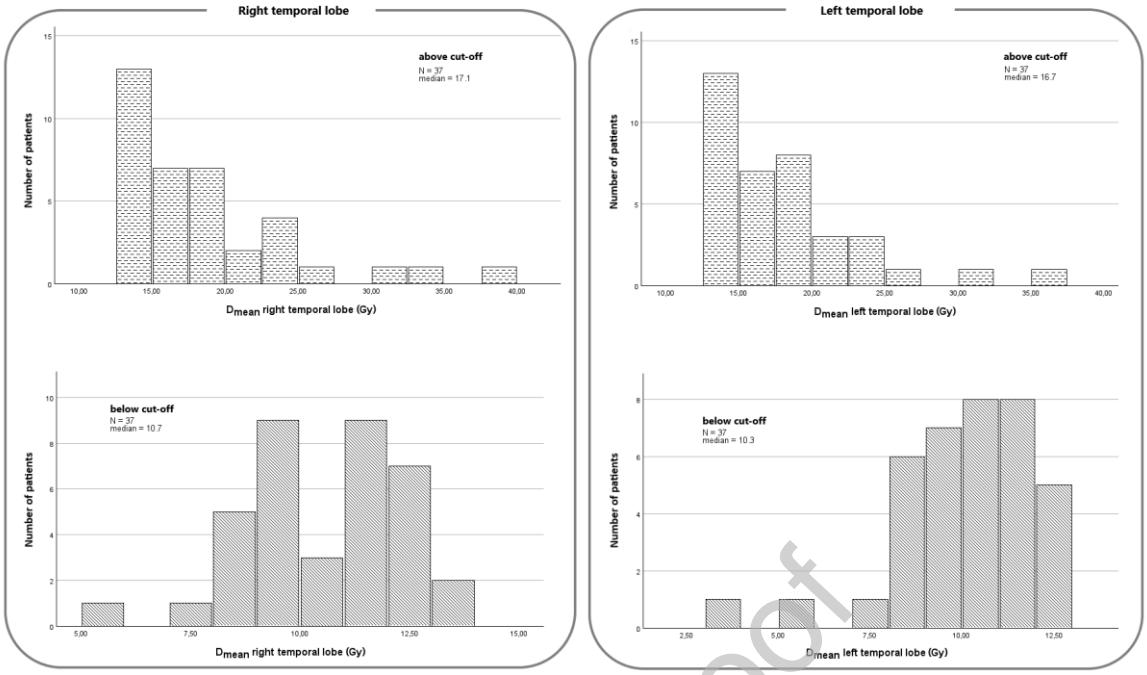

Figure 4. Distribution of the D_{mean} values of the temporal lobes in relation to the subgroups "below" and "above" the cut-off value (see Figure 3A+B): left temporal lobe (≤ 12.7 Gy or > 12.7 Gy); right temporal lobe (≤ 13.2 Gy or > 13.2 Gy). The D_{mean} value of the temporal lobes and the corresponding number of patients are illustrated for each subgroup. Median values are provided for detailed comparison of the subgroups (below vs. above): left 10.3 Gy vs. 16.7 Gy and right 10.7 Gy vs. 17.1 Gy. Abbreviations: D_{mean}, mean dose; N, number; Gy, Gray

Characteristic	N = 74	%
Age at diagnosis, y, median	8.13 (range, 0.01-17.39)	
Gender, female	42	56.8
Histology		
Adamantinomatous	68	91.9
NOS	6	8.1
Hypothalamic involvement		
Typ 0	5	6.8
Typ 1	27	36.5
Typ 2	42	56.8
Hydrocephalus at diagnosis	26	35.1
CSF-Shunting	14	18.9
Cyst-Reservoir	23	31.1
Surgery at diagnosis		
GTR	6	8.1
STR	62	83.8
Biopsy/cyst aspiration	6	8.1
Number of surgical interventions*, median	2 (range, 1-5)	
1	15	20.3
2	35	47.3
3	16	21.6
4	7	9.5
5	1	1.4
Patient with metastasis	1	1.4
Age at RT, y, median	9.21 (range, 3.38-17.52)	
Time from 1st diagnosis to RT, m, median	9.68 (range, 1.31-113.35)	
RT duration, d, median	42 (range, 37-50)	
RT in sedation	16	21.6
Timing of RT		
Initial / first event	18	24.3
At relapse/progression	56	75.7
PBT technique		
PBS	63	85.1
with aperture	4	5.4
US	9	12.2
US+PBS	2	2.7
Use of apertures	15	20.3
Initial tumour size, cc, median	17.64 (range, 3.07-300.59)	
GTV, cc, median	3.43 (range, 0.60-65.28)	
CTV, cc, median	26.21 (range, 9.67-197.93)	
PTV, cc, median	54.17 (range, 21.36-328.80)	

Table 1. Patient characteristics

*Total number of cranial surgeries before PBT including tumour resections, procedures due to hydrocephalus and/or cyst enlargement, reservoir implantation or shunt replacement. Abbreviations: NOS, not otherwise specified; CSF, cerebrospinal fluid; GTR, gross total resection; STR,

subtotal resection; RT, radiotherapy; PBS, pencil beam scanning; US, uniform scanning; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume

Organ at risk	D_{max} (range) in Gy (RBE)	D_{mean} (range) in Gy (RBE)
Optic nerve		
Right	53.61 (44.85-55.65)	26.44 (3.66-50.72)
Left	53.56 (38.95-56.85)	27.29 (3.37-49.70)
Chiasm	54.01 (52.55-57.19)	52.91 (51.58-55.21)
Pituitary	55.03 (53.60-56.77)	54.21 (19.33-55.42)
Hypothalamus	54.95 (53.63-56.81)	53.89 (26.68-55.16)
Brainstem	54.48 (52.29-57.16)	27.14 (7.22-51.68)
Cochlea		
Right	13.86 (0.01-55.81)	5.52 (0.00-53.69)
Left	14.66 (0.19-51.52)	5.59 (0.02-43.07)
Temporal lobe		
Right	54.78 (35.82-56.86)	13.17 (5.20-39.82)
Left	55.27 (51.12-57.00)	12.68 (3.17-35.46)
Hippocampus		
Right	48.08 (22.76-55.61)	18.96 (9.04-53.63)
Left	49.46 (17.93-56.33)	19.71 (4.82-51.82)

Table 2. Dose distribution to organs at risk

Abbreviations: D_{max}, maximum dose; D_{mean}, mean dose; RBE, relative biologic effectiveness;

Adverse events since diagnosis until last follow-up of 74 patients [§]																
AE	Visual impairments		Psychiatric disorders		Facial nerve disorders		Cognitive impairments		Headaches		Fatigue		Ataxia		Other	
Grade	Pre RT	Post RT	Pre RT	Post RT	Pre RT	Post RT	Pre RT	Post RT	Pre RT	Post RT	Pre RT	Post RT	Pre RT	Post RT	Pre RT	Post RT
0	32 (43)	32 (43)	74(100)	73 (99)	70 (95)	71 (96)	68 (92)	59 (80)	58 (78)	53 (72)	62 (84)	50 (68)	70 (95)	71 (96)	74(100)	73 (99)
1-2	27 (36)	29 (39)	0 (0)	0 (0)	3 (4)	2(3)	7 (9)	15 (20)	16 (22)	21 (28)	12 (16)	24 (32)	3 (4)	2(3)	0 (0)	0 (0)
3	5 (7)	4 (5)	0 (0)	0 (0)	1 (1)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
4	10 (14)	9 (12)	0 (0)	1 (1)											0 (0)	0 (0)
5				0 (0)												1 (1)
Conditions pre- vs. post RT [§]*																
improved	10 (14)		0 (0)		3 (4)		5 (7)		12 (16)		8 (11)		2 (3)		0 (0)	
new or deteriorated	4 (5)		1 (1)		2 (3)		15 (20)		19 (26)		21 (28)		1 (1)		1 (1)	
stable	32 (43)		0 (0)		1 (1)		1 (1)		2 (3)		3 (4)		1 (1)		0 (0)	

Table 3. Adverse events after multimodal treatment in childhood craniopharyngiomas

§ Data are presented in numbers, percentage in brackets

*post RT = at the time of last follow-up

Abbreviation: AE, adverse event; RT, radiotherapy