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CLINICAL INVESTIGATION

Outcome After Modern Proton Beam Therapy in Childhood Craniopharyngioma: Results of the Prospective Registry Study KiProReg

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

Methods and Materials: Within the prospective registry study "KiProReg" (DRKS0000536), data of 74 childhood patients with CP, receiving PBT between August 2013 to June 2022 were eligible. Late toxicities were analyzed according to the grading system of the Common Terminology Criteria for Adverse Events, version 4.0.

Results: Median follow-up since first diagnosis was 4.3 years (range, 0.8-14.7). In addition, 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. The median total dose and initial tumor volume were 5400 cGy relative biologic effectiveness (RBE) and 17.64 cm^3 (range, 3.07-300.59), respectively. The estimated ($\pm$SE) 3-year overall survival, progression-free, and cystic failure-free survival rate after PBT were 98.2% ($\pm$1.7), 94.7% ($\pm$3.0), and 76.8% ($\pm$5.4), respectively. All local failures (n = 3) were in-field relapses necessitating intervention and occurred exclusively in patients receiving PBT at progression or recurrence. Early cystic enlargements after PBT were typically asymptomatic and self-limiting. Fatigue, headaches, vision disorders, obesity, and endocrinopathies were the predominant late toxicities. No high-grade ($\geq$3) new-onset visual impairment or cognitive deterioration occurred compared with baseline. The presence of cognitive impairments at the end of follow-up correlated with size of the planning target volume (P = .034), D_{mean} dose to the temporal lobes (P = .032, P = .045) and the number of surgical interventions before PBT (P = .029).

Conclusions: Our findings demonstrate favorable local control rates using modern PBT with acceptable late toxicities. Cyst growth within 12 months after radiation therapy is typically not associated with tumor progression. Longer follow-up must be awaited to confirm results. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/)

Introduction

Craniopharyngiomas (CPs) are benign intracranial neoplasms. Reported incidence rates range from 0.5 to 2.5/10[6] population per year, with 30% to 50% occurring during childhood and adolescence.[1,2] Since the fifth edition (2021) of the World Health Organization classification of central nervous system tumors, CPs are divided into 2 distinct tumor types (adamantinomatous CPs and papillary CPs) given their different characteristics.[3] Adamantinomatous CP represent the majority of CPs with onset during childhood.[4] The tumors are typically located in the sellar region and thereby in close proximity to sensitive critical organs, such as optic chiasm and neuroendocrine structures. Adamantinomatous CP in particular tends to form cysts with sometimes extreme, space-occupying dimensions[5] leading to hormonal deficits, visual impairments, and other physical limitations before treatment.[6,7]

Current treatment options include either complete resection or a limited surgical strategy followed by radiation therapy (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 tumor control, preventing further morbidity and maintaining a high health-related quality of life (QoL) is of high priority.

Although survival rates (overall survival [OS] and progression-free survival [PFS]) after gross total resection (GTR) or subtotal resection (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 effect 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 pediatric patients with CP.[8,20] PBT after surgery achieved promising results in terms of OS and PFS.[13,17,18,21,22] Limited data are 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.

Methods and Materials

Patients were eligible for this analysis if enrolled in the prospective registry study "KiProReg" (German Clinical Trial Register; DRKS-ID: DRKS00005363). Informed consent of their legal guardian(s) was obtained at time of initial presentation at the treatment center. 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 "KiProReg" who received PBT between August 2013 and June 2022 was available for this analysis. Ethical approval (21-10088-BO) 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 follow-up data were not available (Fig. 1). Eventually, data of 74 patients were analyzed. Treatment concepts were performed according to the German KRANIOPHARYNGEOM 2007 trial (n = 59) and KRANIOPHARYNGEOM 2019 Registry (n = 15), respectively.

Treatment planning

Children were typically positioned in supine position and immobilized by a thermoplastic mask on a head frame. Planning softwares were RayStation up to version 10B (Ray-Search Laboratories AB, SE-104 30) and XIO (Elekta), respectively. Target volume delineation was based on planning CT and pre- and postsurgery coregistered diagnostic MRI. Gross tumor volume was defined as the residual tumor (solid and cystic tumor components demonstrated on MRI with contrast enhanced T1- and T2-weighted images) or the tumor bed after surgery. The clinical target volume (CTV) had a uniform margin of 0.5 cm but was manually corrected in the proximity of anatomic barriers and was reduced to 0 to 0.3 cm when invasion was unlikely. Areas expected to be at low risk for recurrence, such as regions with resected cyst walls or tumor bed of the primary tumor in late recurrences, were individually excluded from the CTV after discussion with study center/reference radiation therapy. 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 optimized 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 to 0.5 cm, depending on expected cyst growth. The
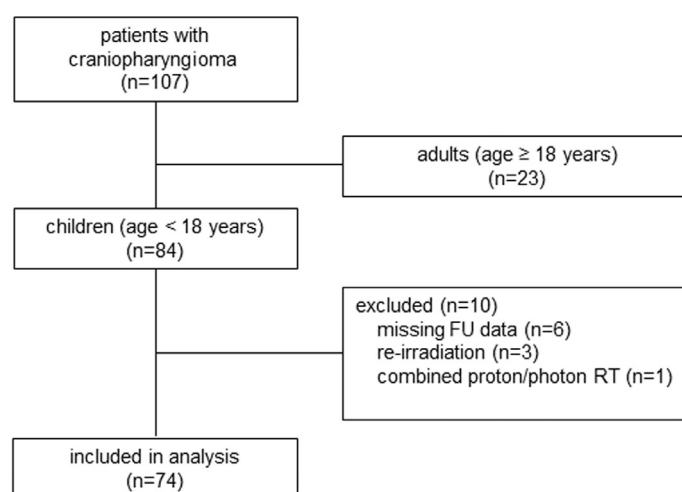
Fig. 1.   Flowchart: Presentation of the inclusion and exclusion criteria of the conducted analysis, including the associated patient numbers. *Abbreviations:* FU, follow-up; RT, radiation therapy

prescribed dose coverage of the PTV generally required that at least 95% of the volume should receive a dose of at least 5130 cGy (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 German KRA-NIOPHARYNGEOM 2007 trial and KRANIOPHARYNG-EOM 2019 Registry 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 utilized 2 to 3 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 to achieve dose limitations. For patients treated with US, a treatment plan with 2 to 4 fields was created. Image guided radiation therapy was performed using orthogonal kV-imaging in 2 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, brain stem, 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 tumor removal if confirmed by neuroradiologic imaging (MRI). Any tumor 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 tumor 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 tumor 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's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.[24] CTCAEs recorded during follow-up belonged to the following system organ classes: "ear and labyrinth disorders," "eye disorders," "neoplasms benign, malignant and unspecified (including cysts and polyps)," "vascular disorders," "endocrine disorders," and "surgical and medical procedures." General toxicity data refer to all grade 1 to 2 AEs that occurred in at least 10% of patients and all high-grade (≥3) AEs at baseline and during follow-up. Visual field and visual acuity impairments were summarized under the term "vision disorders," and memory impairment and cognitive disturbance were summarized under the term "cognitive impairments" for statistical analysis. According to the "KiProReg" registry questionnaires and face-to-face follow-up consultations with a radiation oncologist from our center were conducted. If an in-person follow-up 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. Follow-up 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 follow-up, the questionnaire were filled in by themselves. Noted toxicities within questionnaires were reviewed and quantified by radiation oncologist during the follow-up consultations. The questionnaire included specific questions regarding noticeable changes in cognitive perception or performance (eg, orientation, attention, or concentration disturbances)

and "memory impairment (retentiveness)." However, neuropsychological assessments were not routinely collected according to the registry protocol. Except for imaging, all follow-up consultations and examinations were performed within 3-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 sex-adjusted body mass index (BMI) standard deviation scores (BMI-SDS).[25,26] Respective reference data were used for patients ≤18[26] and >18 years of age.[27] Ophthalmologic examinations (visual field and visual acuity) were performed according to the standards of the referring hospital. These reports were retrospectively analyzed 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 German KRANIOPHARYNG-EOM 2007 trial and KRANIOPHARYNGEOM 2019 Registry were sent to a neuroradiological reference center for review. Patients were defined as lost to follow-up in case of unsuccessful attempts of inviting patients to their annual follow-up and of unfruitful attempts of receiving reports of referring oncologists, respectively, 3 times in a row, or in case of patients refusing to further participate in the registry.

Survival

OS, 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 Pediatric Neuro-Oncology (RAPNO) committee,[28] as any solid tumor 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. Infield 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 follow-up 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 follow-up was used for censoring in PFS and CFFS, respectively.

Statistical analysis

Distribution and relationship of attributes were calculated and compared using cross tables and χ^2 tests. Bivariate Pearson's correlation was performed on the continuous variables. To analyze the association between most frequently occurring late toxicities, the initial tumor size, target volumes (CTV, PTV), D_{mean} of OARs, and age at RT, a threshold search was conducted to divide quantitative data into 2 classes of qualitative variables using the mean value (less than or equal to the mean or greater than the mean). Used mean values are shown in the Tables 1 to 3. 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 $P \leq .05$ without adjustment for multiple testing. Statistical analysis was performed using IBM SPSS Statistics software, version 29 (IBM Corp) and R statistic software version 4.1.2 (The R Foundation for Statistical Computing).

Results

Patients and treatment characteristics

The median follow-up 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. In addition, 48.6% of the cohort had a follow-up longer than 3 years since PBT. Sixty-eight patients (91.9%) underwent surgical tumor 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 received a diagnosis of an implantation metastasis in the left ventricle besides the primary disease at the time after initial operation. Primary tumor site and the metastasis received local PBT with 54 Gy at 1.8 Gy per day. The treatment time course of 2 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 tumor size was associated with larger size of gross tumor volume, CTV and PTV ($P < .001$) and higher D_{mean} values of the OARs nervi optici, cochleae, brain stem, temporal lobes, and hippocampi ($P < .001$; $P \leq .005$; $P < .001$; $P < .001$; $P < .001$). A large CTV and PTV was associated with higher D_{mean} values of the OARs nervi optici, cochleae, temporal lobes, hippocampi, brain stem, and chiasm ($P \leq .002$; $P < .001$; $P < .001$; $P < .001$; $P < .001$; $P < .001$). There was no association between initial tumor 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 tumor-associated comorbidities 16.36 month after completion of PBT. The estimated 3-year

Table 1   Patient characteristics

| Characteristic	N = 74	%
Age at diagnosis, y, median	8.13 (range, 0.01-17.39)	
Sex, female**	42	56.8
Histology		
Adamantinomatous	68	91.9
NOS	6	8.1
Hypothalamic involvement		
Type 0	5	6.8
Type 1	27	36.5
Type 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
No. 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 tumor 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)	

* Total number of cranial surgeries before PBT including tumor resections, procedures due to hydrocephalus and/or cyst enlargement, reservoir implantation or shunt replacement.
** The use of the term "sex" in the text refers to the biological aspect.
Abbreviations: CSF = cerebrospinal fluid; CTV = clinical target volume; GTR = gross total resection; GTV = gross tumor volume; NOS = not otherwise specified; PBS = pencil beam scanning; PTV = planning target volume; RT = radiation therapy; STR = subtotal resection; US = uniform scanning.

Table 2   Dose distribution to organs at risk

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)
Brain stem	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)

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

PFS rate was 94.7% (±3.0). We observed 3 tumor progressions, each characterized 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 after PBT. The patients were symptomatic and required surgical intervention. The local failures in the group of patients receiving PBT at primary treatment compared with 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 3 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 tumor, size of target volumes (CTV/PTV), resection status, number of surgical intervention appointments before PBT, implanted cyst reservoir, or tumor progression were observed.
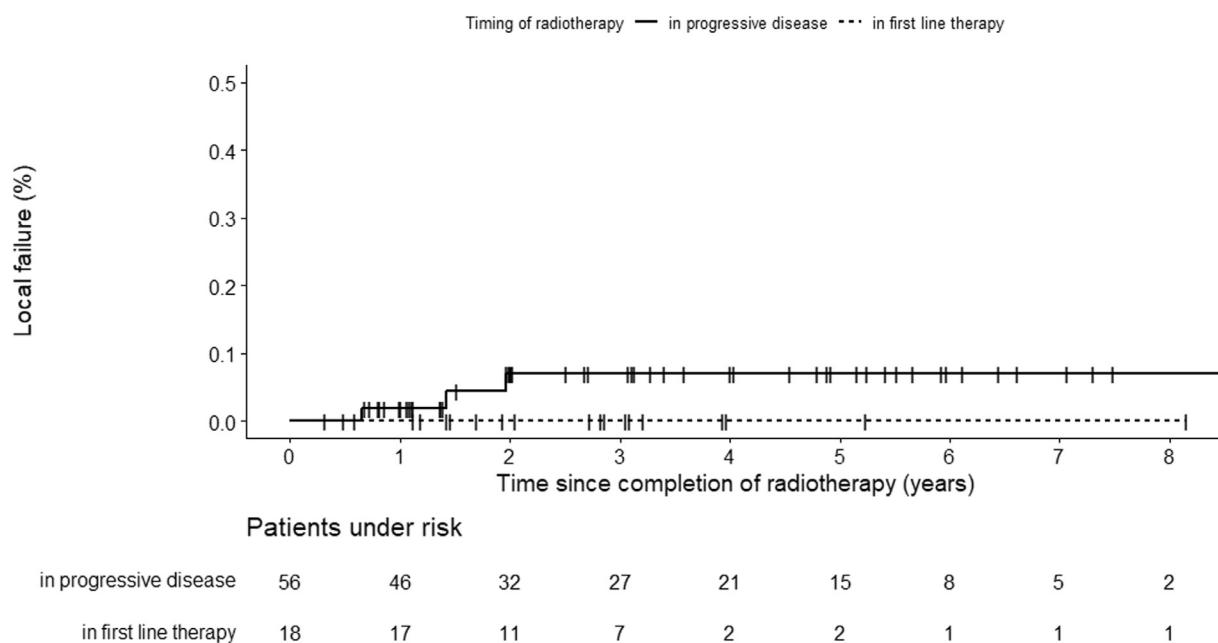
Fig. 2.   Local failure after radiation therapy. Local failure rates since completion of radiation therapy, comparing radiation time points at first event or at relapse/progression showing estimated 3-year rates of 0% and 7% (±3.9), respectively.

AEs

Considering late AEs after PBT, only 2 new AEs ≥ grade 3 occurred during follow-up (Table 3). One patient with pre-existing seizures and mental vigilance disturbances after multiple surgeries developed progressive brain stem symptoms, which could not be clearly attributed to irradiation, and finally died 16 months after completion of PBT. Another patient received a diagnosis of 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 intrafamily conflicts. No other onsets ≥ grade 3 AEs were reported regarding cognitive impairment, vision disorders or neuroendocrine deficits. Pre- and post-PBT conditions are presented in Table 3. After interdisciplinary therapy, 57% of patients experienced visual impairments, 32% fatigue, 28% headaches, and 20% cognitive impairments, respectively. Effect of timing of PBT, HI, size of initial tumor, size of target volumes, OAR D_{mean} values, extent of resection, number of surgical interventions before PBT, or age at PBT was analyzed. The occurrence of vision disorders since diagnosis (n = 42) was associated with the timing of PBT ($P = .021$), showing more deficits in the group of patients irradiated at progression/recurrence compared with those irradiated at first diagnosis. The onset or deterioration of cognitive impairment (n = 15) after PBT was associated with the size of PTV ($P = .034$), D_{mean} dose to the temporal lobes (right: $P = .032$; left: $P = .045$) and the number of surgical interventions before PBT ($P = .029$), showing more deficits in patients with larger PTV, higher D_{mean} values and number of interventions (Fig. 3, A-D). Because of 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 (Fig. 3A and 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 follow-up was available in 70 patients. Endocrine deficits were already numerous at baseline and continued to increase during follow-up. The most common deficits, in descending order (percentage pre/post-RT), were thyroid-stimulating hormone deficiency (84.3/90), adrenocorticotropic hormone deficiency (80/85.7), growth-hormone-deficiency (64.3/82.9), diabetes insipidus (74.3/77.1), and follicle-stimulating hormone/luteinising hormone deficiency (38.6/44.3). The sex-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 4 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 4 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-center cohort published to date on patients with childhood

Table 3 Adverse events after multimodal treatment in childhood craniopharyngiomas

Adverse events since diagnosis until last follow-up of 74 patients*

AE Grade	Visual impairments		Psychiatric disorders		Facial nerve disorders		Cognitive impairments		Headaches		Fatigue		Ataxia		Other	
	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)	0 (0)											1 (1)	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)	

* Post-RT = at the time of last follow-up.
† Data are presented in numbers, percentage in brackets.
Abbreviation: AE = adverse event; RT = radiation therapy.

CP treated with PBT using predominantly PBS. Although, there is only limited PBT data available on large pediatric patient cohorts, our results confirm previously published findings using different PBT techniques regarding 3-year OS and PFS rates ranging from 94.1% to 100% and 91.7% to 96.8%, respectively.[17,18,22] When comparing survival with previous proton therapy cohorts, analysis-related characteristics must be considered. In addition, 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 with 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 analyzed receiving PBT after surgery but only the growth of solid tumor components were 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 the study by Bishop et al[17] with nodular progression-free survival rate as an indicator for PFS, their estimated 3-year rate was 91.7% after a median follow-up of 33 month. This calculation is conservative when considering that in their PBT cohort, 3 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 must be made with caution. We could demonstrate a high local tumor control rate at an early follow-up stage. Trends beyond 3 years after PBT cannot be validly derived from our short follow-up 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 tumor progression as an increase of $\geq 25\%$ in at least 2 consecutive imaging evaluations, beginning 2 to 3 years after treatment. The RAPNO working group does not consider an intervention-requiring increase in cystic tumor 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. Eighteen 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
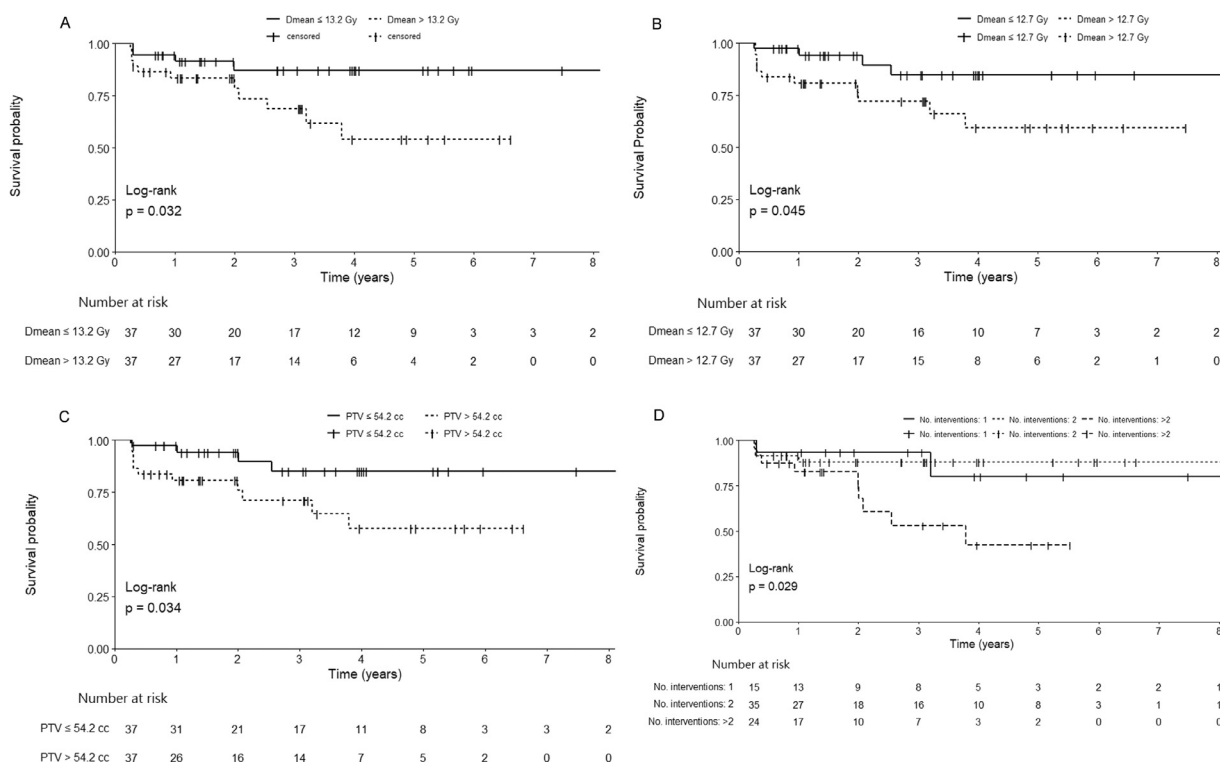
Fig. 3. Cognitive deficit-free survival rates. Onset or deterioration of cognitive impairment after proton beam therapy (PBT) in years, depending on various treatment modalities as risk factors: D_{mean} dose to the temporal lobes [right lobe: (A); left lobe: (B)], the size of planning target volume (PTV) (C), and the number of surgical interventions before PBT (D). In 15 patients, cognitive impairments were reported and classified as grade 1 or 2 according to Common Terminology Criteria for Adverse Events, version 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 ($\leq$13.2 or $>$ 13.2 Gy) and D_{mean} left temporal lobe ($\leq$12.7 or $>$12.7 Gy); mean PTV ($\leq$54.2 or $>$54.2 cc). The number of surgical interventions before PBT was divided into 3 groups: only one intervention, 2 interventions, or more than 2 interventions. *Abbreviations:* D_{mean} = mean dose; No. = number.

tumor 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 most patients (83.8%) received STR + PBT. However, there were no differences in outcome compared with 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 must rely on QoL and reducing treatment-related morbidity. Fouda et al[14] concluded that irradiation-induced morbidities and aggressive surgery-related morbidities 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

with GTR alone. Besides, technical developments also need to be considered. Compared with 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 optimized 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 center.[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 with 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. Optimizing 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
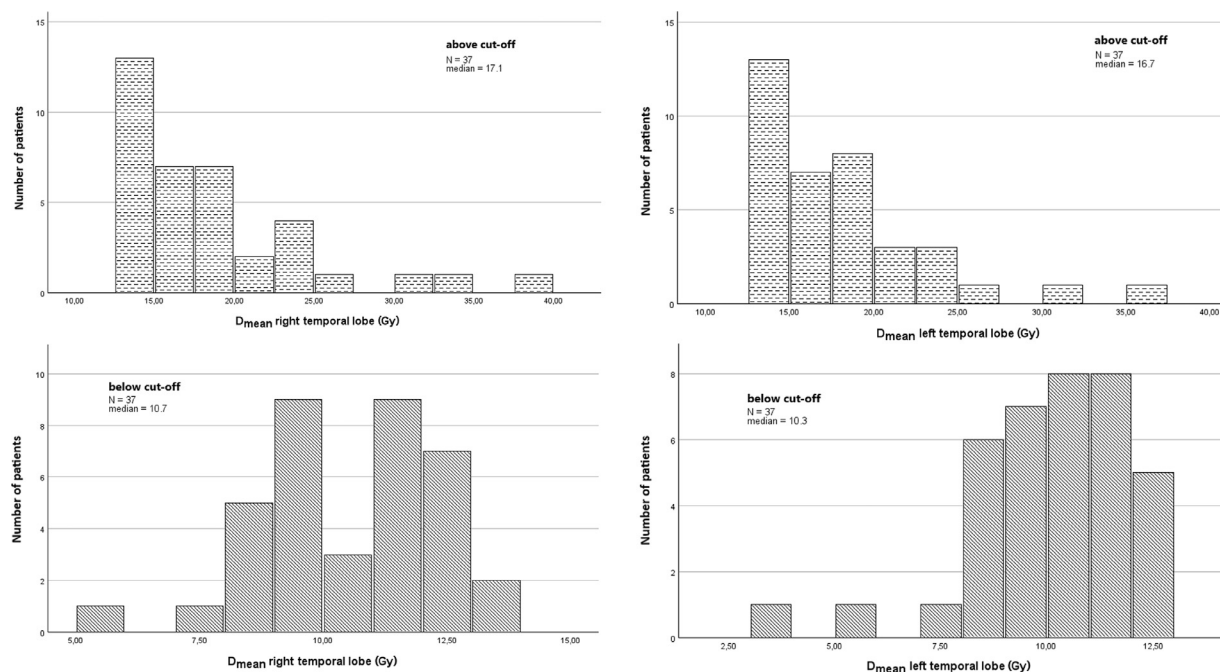
Fig. 4. Distribution of the D_{mean} values of the temporal lobes in relation to the subgroups "below" and "above" the cut-off value (see Fig. 3A and B): left temporal lobe (≤12.7 Gy or >12.7 Gy); right temporal lobe (≤13.2 Gy or >13.2 Gy). The D_{mean} value of the temporal lobes and the corresponding number of patients are illustrated for each subgroup. Median values are provided for detailed comparison of the subgroups (below vs above): left 10.3 versus 16.7 Gy and right 10.7 versus 17.1 Gy. *Abbreviations:* D_{mean} = mean dose; N = number.

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 to 1 cm.[13,18] The recently published study by Edmonston et al,[40] observing 101 childhood CP patients after photon-based conformal radiation therapy, found a significant association of larger PTV and increased risk of vasculopathy, after a median follow-up time of 14.9 years. Despite our comparatively early results regarding follow-up time, we found that cognitive impairments were more likely over time in patients with larger PTVs. Even if target volumes will highly depend on tumor 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 noninvolved healthy tissue, especially in the mid- and low-dose ranges. We could also demonstrate a correlation of the initial tumor 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 tumors 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 tumor entity.[16,42-44] In our cohort, only 2 high-grade (≥3) late toxicities were observed and no new-onset or deterioration of ≥ grade 3 visual or cognitive impairment occurred during follow-up. Within our cohort, almost all patients presenting with an elevated or pathologic 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 before the initiation of RT.

However, a crucial aspect for the utilization of PBT in suprasellar tumors 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 2 trial, showing a decrement in intelligence quotient by 1.09 points/y and a decline in adaptive behavior by 1.48 points/y when photon therapy was used compared with PBT. In contrast to their historical data post conformal radiation therapy, 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 follow-up compared with values around 16.7 Gy (left) and 17.1 Gy (right). These findings suggest a substantial effect 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 nonspecific and do not measure IQ alone but can be used as general indicators for cognitive impairments. Tumor 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. Furthermore, our results suggest that the tumor-dependent PTV size also allows conclusions to be drawn about the occurrence of neurocognitive deficits within the follow-up. Data from our cohort indicate 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 tumor, host, and treatment factors. Keeping previous published results in mind, those investigations could help interpret and explain our findings on cognitive decline. However, we must note that our evaluation does not allow a differentiated statement on cognitive performance, as no specific neuropsychological assessments were performed. Our analysis of tumor 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 must 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 recognized and new insights gained from which hypotheses for future research can be derived.

Regarding QoL and the development of treatment sequelae, the timing of RT, directly adjuvant or in case of recurrence or progression is still controversial and may affect 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 must be interpreted with caution. To draw conclusions regarding differences in subjectively perceived QoL depending on the

timing of RT, patients in the German KRANIOPHARYNG-EOM 2007 trial were randomized after incomplete tumor resection to immediate postoperative RT versus RT upon progression. The randomization was stopped for futility in 2016 and only minor differences in terms of QoL were observed between the 2 treatment approaches.[19] Regarding QoL after incomplete resection (n = 41) they stated that RT predominantly (65.9%) administered due to progression of residual tumors 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 ($P = .017$ and .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 radiation therapy avoiding repetitive surgeries. However, timing of radiation and extent of resection need to be individually evaluated over the course of disease within an MDT regarding potential treatment toxicity versus an increased risk for recurrence.

We must acknowledge several limitations of our study. Although the data were collected within a standardized, 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 follow-up 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 follow-up. In addition, standardized neurocognitive examinations were not part of the registry's regular program.

Conclusion

Outcomes of children with CP after surgery and PBT showed excellent local tumor 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 follow-up. 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 utilization of recent technical developments 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 pediatric patients with CP, we have made the decision to conduct a dedicated analysis of the substantial data volume to explore this topic comprehensively. Additional research in prospective trials is necessary, especially regarding the assessment of QoL and neurocognitive functions, but also optimal sequencing of treatment modalities. Longer follow-up must be awaited to evaluate the full scope of late effects including cerebrovascular events and secondary malignancies.

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