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REVIEW

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Proton beam therapy for craniopharyngioma: a systematic review and meta-analysis

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Abstract

Background Craniopharyngioma is a rare and slow-growing benign sellar or parasellar epithelial tumor. The number of patients receiving proton beam therapy (PBT) has increased. This study aimed to systematically evaluate and analyze the comprehensive evidence regarding the safety and efficacy of PBT for craniopharyngioma.

Methods We searched four databases: the Cochrane Library, PubMed, Embase, and Web of Science. The period was from their inception to February 16, 2024. Two researchers independently screened the literature and extracted data.

Results Among 486 candidate articles, eight studies were included in our study. Exactly 393 patients with craniopharyngioma underwent PBT in these studies. These studies reported data on survival and toxicity. The median sample size was 42.5 patients. The median age was 9.1–37 years; the female proportion was 48.9%, and the median follow-up time was 29–91.4 months. All patients were treated once daily, five times a week, with a fraction of 1.8 Gy (RBE) per session. The median total dose was 54.0 Gy (RBE). The local control rates at 3 and 5 years in these studies were 99% and 93%, respectively. The overall survival rates at 3 and 5 years in these studies were both 100%. The incidence of acute and late toxicities was mainly grade 1–2. The main late toxicities included vascular and visual toxicities, hypothalamic obesity, endocrinopathy, and panhypopituitarism.

Conclusions PBT for craniopharyngioma, especially in children and adolescents, has shown impressive local control and acceptable acute and late toxicities.

Keywords Craniopharyngioma, Proton beam therapy, Systematic review and meta-analysis

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Introduction

Craniopharyngioma is thought to originate from squamous cell remnants in Rathke's pouch (the embryological precursor to the pituitary gland). It is a rare and slow-growing sellar or parasellar benign epithelial tumor [1, 2]. It is defined as a World Health Organization (WHO) grade I neoplasm and represents 2–5% of all primary intracranial tumors [2].

Surgery has long been the primary treatment strategy. Gross tumor resection (GTR) is difficult if the tumor is adjacent to the visual pathway, the hypothalamic-pituitary axis, or the cerebrovascular system [3]. GTR often leads to severe hypothalamic damage with various unacceptable complications [4]. Therefore, to avoid hypothalamic morbidity, safe sub-total resection (STR) is usually performed in clinical practice.

Studies have shown that patients undergoing STR combined with radiotherapy (RT) can achieve survival outcomes similar to GTR [5, 6]. In addition, STR combined with RT can not only preserve the hypothalamus but also reduce the risk of long-term severe obesity and diabetes insipidus in children [7, 8]. Most patients with craniopharyngioma are children, and radiation toxicity is of utmost concern for radiation oncologists, especially in young patients with a long life expectancy [8]. Compared to conventional X-ray RT (XRT), proton beam therapy (PBT) has superior radiophysical properties [9–11]. It can deposit the majority of the dose in the "Bragg peak" region, providing a more favorable dose distribution than photons [9–11]. Moreover, PBT can deliver a high dose to the tumor area while protecting the organ at risk from radiation-induced toxicities [9–11].

Currently, studies on PBT for craniopharyngiomas have mainly been reported as case series. However, the sample size was small, and its safety and efficacy were unclear. Therefore, this study aimed to systematically evaluate and analyze the comprehensive evidence for PBT treatment of craniopharyngioma and provide the latest evidence for PBT clinical treatment, guideline formulation, and policy implementation.

Materials and Methods

Literature identification

The procedure was conducted as previously described [12]. The review protocol is registered in PROSPERO (CRD42023444348).

Search strategy

We searched four databases: the Cochrane Library, PubMed, Embase, and Web of Science. The period was from their inception to February 16, 2024. The search strategies were determined according to the PRISMA guidelines and recommendations [13]. The search terms were as follows: "Craniopharyngioma OR Craniopharyngiomas OR Craniopharyngioma*" AND "Proton therapy OR Proton OR Proton Therap* OR Proton Beam Therap* OR Proton Beam OR Proton Beam Radiation Therapy." The references included in the studies were traced simultaneously.

Inclusion and exclusion criteria

The articles were independently screened by MD and ZL. The inclusion criteria were as follows: (a) patients were clinically or pathologically diagnosed with craniopharyngioma; (b) all the patients received PBT; (c) the survival outcome data included local control (LC) and overall survival (OS) rates; and (d) the toxicity associated with PBT was reported.

The exclusion criteria were as follows: (a) duplicate publications; (b) patients who received treatment only with photons, carbon ion RT, and other particles; (c) comments, abstracts, case reports, protocols, reviews, meta-analyses, and letters; (d) receiving PBT re-irradiation; (e) incomplete data; and (f) clinical studies with fewer than 10 patients.

Data extraction

ZL and QL independently performed the literature screening and data extraction. All results were reviewed by WD. Disagreements were discussed among the three investigators until a consensus was reached. Data were extracted as described previously [12].

Quality and bias assessments

The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess the quality and bias of the case series [14]. RL and MD independently completed the literature quality and bias assessments. Disputes were resolved by a third reviewer (DW) with answers of yes, no, unclear, or not applicable. The evaluation indicators and outcomes are presented in Table 1.

Statistical analysis

Descriptive statistics were used to summarize the baseline variables and incidence of toxicity. Data descriptions included frequencies and percentages for dichotomous data and means with standard deviations or medians with interquartile ranges for continuous data. The case series studies were conducted under different conditions. Thus, we used a random effects model to provide an overall summary estimate. We computed the proportions with 95% confidence intervals (CIs) to estimate the effect sizes for continuous outcomes. All analyses were performed using STATA version 14.0 (StataCorp, College Station, Texas, USA).

Table 1 Assessment of risk of bias in included studies

Study	Criterion									
	a	b	c	d	e	f	g	h	i	j
USA										
Bishop (2014) [15]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Luu (2005) [16]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Merchant (2023) [17]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Rutenberg (2020) [18]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Jimenez (2021) [19]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
UK										
Ajithkumar (2018) [20]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Friedrich (2023) [21]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
France										
Beddok (2023) [22]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes

(a) Were there clear criteria for inclusion in the case series?;(b) Was the condition measured in a standard, reliable way for all participants included in the case series?;(c) Were valid methods used for identification of the condition for all participants included in the case series?;(d) Did the case series have consecutive inclusion of participants?;(e) Did the case series have complete inclusion of participants?;(f) Was there clear reporting of the demographics of the participants in the study?;(g) Was there clear reporting of clinical information of the participants?;(h) Were the outcomes or follow-up results of cases clearly reported?;(i) Was there clear reporting of the presenting sites'/clinics' demographic information?;(j) Was statistical analysis appropriate?

Results

Study selection and characteristics

As illustrated in Fig. 1, we retrieved 486 candidate articles, including 141 from PubMed, 204 from Web of Science, 138 from Embase, and three from the Cochrane Library. There were 196 duplicate studies. A total of 239 papers were letters, comments, protocols, reviews, meta-analyses, case reports, photons, brachytherapy, and irrelevant topics. We screened 51 related studies for full-text eligibility. After eliminating 43 studies with no detailed data, eight were finally included in our systematic review. These eight studies originated from three countries: the United States ($n=5$), the UK ($n=2$), and France ($n=1$) [15–22]. All eight included articles were retrospective studies that reported data regarding survival and toxicity.

A total of 393 patients with craniopharyngioma were included, with a sample size ranging from 14 to 94 patients, a median age ranging from 9.1 to 37 years, and a median follow-up time ranging from 29 to 91.4 months (Table 2). The proportion of female and male patients was 48.9% and 51.1%, respectively (Table 2).

Clinical features

As presented in Table 3, 393 patients were diagnosed with craniopharyngioma, of which four studies reported on histology (mainly including adamantinomatous and papillary) [18, 19, 21, 22]. Approximately 96.7% of the patients with craniopharyngioma underwent surgery prior to RT, including gross total resection and subtotal resection (Table 3). In addition, seven studies reported reasons for PBT, including definitive RT, postoperative RT, and salvage RT (Table 3) [15, 16, 18–22]. The main details of the tumor size and target volume are presented in Table 3.

PBT

Passive scanning was mainly used for PBT delivery, and the MD Anderson Cancer Center, Massachusetts General Hospital and West German Proton Therapy Centre (Essen) used active/passive scanning (Table 4). For the median total dose, different prescription doses were used at each research center. Overall, the most common median total dose was 54 Gy (RBE), and the most common fraction dose was 1.8 Gy (RBE). The main details of the beam delivery, median total dose, fraction dose, and fractions are presented in Table 4.

LC and OS rate outcomes of PBT

In our systematic review, the meta-analysis results revealed that the LC rate at 3 and 5 years in the studies were 99% (95% confidence interval (CI): 0.98–1.00, $I^2=66.7\%$) and 93% (95% CI: 0.90–0.96, $I^2=0\%$), respectively (Fig. 2). As illustrated in Fig. 3, the OS rates for craniopharyngioma at 3 and 5 years after PBT were 100% (95% CI: 1.00–1.00, $I^2=0\%$) and 100% (95% CI: 1.00–1.00, $I^2=0\%$), respectively.

Toxicity

After PBT for craniopharyngioma, some patients experienced acute and late toxicities, mainly grades 1 and 2 (Table 4) [15–22]. Acute toxicity grade 3 was observed in two studies. The incidence rate was 1–4% [17, 19]. The major acute toxicities included alopecia, cutaneous toxicity, headaches, fatigue, blood disorders (anemia), and

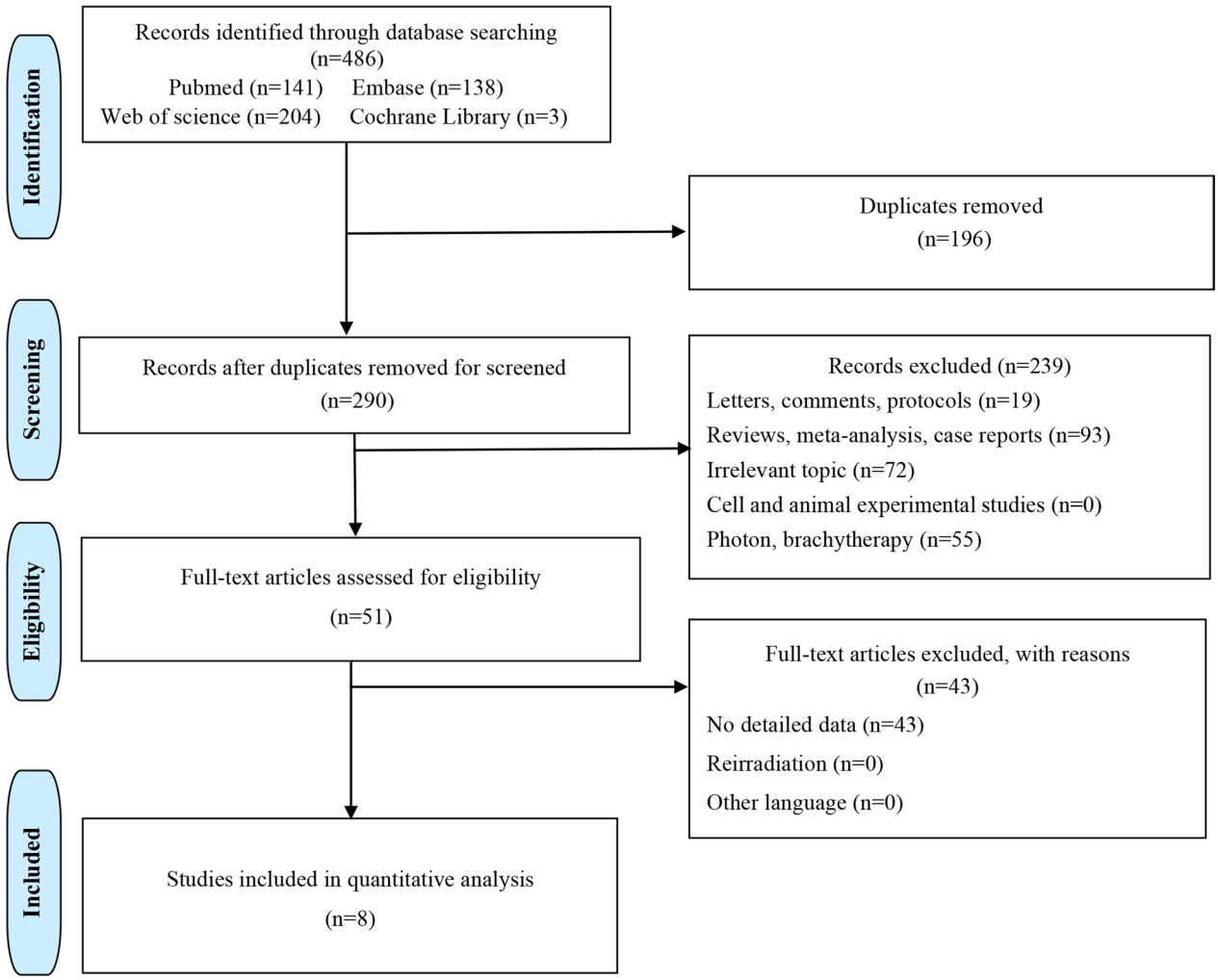

Fig.1 Search results per the PRISMA guidelines

Table 2 Baseline characteristics of included studies

Study	Study type	Institution	Outcomes	Period	No. of patients	Median age (years)	Male/female	Median follow-up (months)
Bishop (2014) [15]	Retrospective	MDACC	Survival, toxicity	1996–2012	21	9.1	9/12	33.1 (10.5–65.6)
Luu (2005) [16]	Retrospective	LLPTC	Survival, toxicity	1991–2000	16	Unclear	10/6	60.2 (12–121)
Merchant (2023) [17]	Retrospective	UFHPTI	Survival, toxicity	2011–2016	94	9.39 (6.39–13.38)	45/49	91.4 (77.8–102.5)
Rutenberg (2020) [18]	Retrospective	UFHPTI	Survival, toxicity	2012–2018	14	28 (22–53)	5/9	29 (17–85)
Jimenez (2021) [19]	Retrospective	MGH	Survival, toxicity	2002–2018	77	9.6 (2.3–20.5)	41/36	57.6 (9.6–187.2)
Ajithkumar (2018) [20]	Retrospective	WPE	Survival, toxicity	2013–2016	16	10.2 (5.4–46.9)	5/11	32.6 (9.2–70.6)
Friedrich (2023) [21]	Retrospective	WPE	Survival, toxicity	2007–2019	64	10.9 (2.5–20.8)	34 /30	76.8 (10.8–175.2)
Beddok (2022) [22]	Retrospective	IC	Survival, toxicity	2006–2018	91	37 (26–51)	52/39	39 (7–147)

MDACC: MD Anderson Cancer Center; LLPTC: Loma Linda Proton Therapy Centre; UFHPTI: University of Florida Health Proton Therapy Institute; MGH: Massachusetts General Hospital; WPE: West German Proton Therapy Centre Essen; IC: Institut Curie

Table 3 Clinical features of all included studies

Study	Type of disease	Histology	Reason for PT	Surgery	Gross total/ Subtotal resection/Other	Tumor size	Target volumes(cc)
Bishop (2014) [15]	craniopharyngioma	NR	Definitive=4 Postoperative=8 Salvage=9	21 (100%)	9/5/7	4.5 cm	NR
Luu (2005) [16]	craniopharyngioma	NR	Postoperative=11 Salvage=5	16 (100%)	NR	1.2-9 cm	NR
Merchant (2023) [17]	craniopharyngioma	NR	NR	90 (96%)	NR	NR	NR
Rutenberg (2020) [18]	craniopharyngioma	Adamantinomatous=11 Papillary=4 Unknown=1	Definitive=1 Postoperative=11 Salvage=2	13 (93%)	NR	NR	NR
Jimenez (2021) [19]	craniopharyngioma	Adamantinomatous=77	Postoperative=30 Salvage=47	77 (100%)	14/46/17	3.6 (1.3-14) cm	NR
Ajithkumar (2018) [20]	craniopharyngioma	NR	Definitive=2 Salvage=14	16 (100%)	NR	NR	PTV (27.8-328.73)
Friedrich (2023) [21]	craniopharyngioma	Adamantinomatous=64	Postoperative=6 Salvage=51	59 (92.2%)	49/10/0	0.1-286.3 cm^3	NR
Beddok (2022) [22]	craniopharyngioma	Adamantinomatous=38 Papillary=12 Unknown=41	Definitive=3 Postoperative=61 Salvage=27	88 (96.7%)	77/11/0	NR	GTV (1.6-7.15) CTV (9.4-22.4) PTV (16.3-34.7)

weight gain [15–22]. Late toxicity grade 3 was observed in two studies, with an incidence of 6–6.3% [17, 22]. Moreover, grade 4 late toxicity (hypernatremia, eye disorders, sepsis, and hyponatremia) was observed in one study with an incidence of 2% [17]. The major late toxicities included vascular disorders, optic neuropathy, hypothalamic obesity, insomnia, frontal lobe encephalomalacia, endocrinopathy (panhypopituitarism, growth hormone deficits, hypothyroidism, adrenal insufficiency, and sexual hormone deficiencies), and cognitive/memory disorders [15–22]. In addition, one study reported a secondary malignancy (radiation-induced) with an incidence of 6.25% ($n=1$) [16]. However, the incidence of secondary malignancy (radiation-induced) was only 0.25% in all the included populations.

Discussion

Given the rarity of craniopharyngiomas, there are currently no evidence-based guidelines and no clear consensus. Craniopharyngioma is most common in children and adolescents [23]. Moreover, surgery and RT are the main treatment strategies [4–6]. However, the balance between treatment effectiveness and long-term complications is of great concern for neurosurgeons and radiation oncologists. The hypothesis that PBT is superior to photon therapy has not been rigorously confirmed [17, 21]; however, some reduction in radiotherapy-associated toxicity has been supported by small-sample dosimetry and clinical studies [10, 24]. We analyzed studies on the efficacy and toxicity of PBT for craniopharyngioma. Our systematic review suggests that PBT for craniopharyngioma result in encouraging LC and OS rates with acceptable acute and late toxicities.

In our systematic review (Table 3), most patients with craniopharyngiomas underwent surgical resection before PBT. In addition, seven studies reported reasons for PBT, including definitive RT, postoperative RT, and salvage RT (Table 3) [15, 16, 18–22]. Previous studies have revealed that patients who undergo GTR and STR combined with RT may achieve survival outcomes similar to those who undergo GTR [5, 6]. Zhang reported the survival results regarding GTR, RT, and STR + RT in 1218 cases of craniopharyngioma [25]. The results suggested that there was no significant difference in the OS or cause-specific death in patients receiving GTR, RT, and STR + RT ($P>0.05$) [25]. Although these data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database, more data are required to validate these findings [25]. A meta-analysis of recurrence rates for craniopharyngiomas showed that although the recurrence rates favored GTR, the difference in recurrence risk between GTR and STR + RT was not significant [6]. In that study, the

Table 4 Survival outcomes, toxicity incidence and prognostic factors on patients of all included studies

Study	Beam-Delivery	Median total dose (GyRBE)	Fractions(n)	Dose/fraction GyRBE	Cyst dynamics	Radiation induced tumor	Local Control	Overall Survival	Toxicity
Bishop (2014) [15]	Passive scanning	50.4 (50.4-54)	28 (28-30)	1.8	Growth=6	0	3-y (91.7%)	3-y (94.1%)	Acute: there were few acute side effects
	Active scanning				Contraction=6 No change=8 Unknown=1				Late: unable to evaluate (20.9-25%)
Luu (2005) [16]	NR	50.4-59.4	28-33	1.8	NR	1 (6.25%)	Crude LC was 93.8%	Crude OS was 81.3%	Acute: there were few acute side effects Late: unable to evaluate (18.8%)
Merchant (2023) [17]	Passive scanning	54	30	1.8	Growth=14	0	3-y (96.8%) 5-y (93.6%)	3-y (100%) 5-y (100%)	Acute: ≤G3 (G3=1%) Late: ≤G4 (G3=6%, G4=2%)
Rutenberg (2020) [18]	Passive scanning	54 (52.2-54)	30 (29-30)	1.8	Growth=2	0	3-y (100%)	3-y (100%)	Acute: ≤G2 (G2=14%) Late: ≤G2 (G2=29%)
Jimenez (2021) [19]	Passive scanning Active scanning	52.2 (45-54)	29 (28-30)	1.8	Growth=10	0	5-y (90.1%)	5-y (97.7%)	Acute: ≤G3 (G3=4%) Late: unable to evaluate
Ajithkumar (2018) [20]	Passive scanning	54 (36–59.4)	30	1.8	Growth=5	0	Crude LC was 93.8%	Crude OS was 100%	Acute: ≤G2 (G2=12.5%) Late: ≤G2 (G2=12.5%)
Friedrich (2023) [21]	Passive scanning Active scanning	54 **(**50.4-54**)**	30	1.8	NR	0	5-y (92.0%)	5-y (98.4%)	Acute: NR Late: ≤G2
Beddok (2022) [22]	Passive scanning	54 (52.2-54)	30 (29-30)	1.8	NR	0	3-y (94.8%) 5-y (92.0%)	3-y (100%) 5-y (100%)	Acute: ≤G2 Late: ≤G3 (G3=6.3%)

recurrence rates regarding GTR, STR + RT, and STR were 17%, 27%, and 45%, respectively [6]. The risk of developing recurrence was not significant for GTR vs. STR + RT (odds ratio [OR]: 0.63, 95% CI: 0.33–1.24, $p = 0.18$) [27]. However, the recurrence risk regarding GTR vs. STR and STR vs. STR + RT were significant, which were (OR: 0.24, 95% CI: 0.15–0.38) and (OR: 0.20, 95% CI: 0.10–0.41), respectively [6]. Based on these findings, there may be no significant difference in survival and recurrence risk between GTR and STR + RT. Therefore, neurosurgeons should seek a balance between efficacy and complications when determining surgical strategies for GTR and STR to avoid substantial treatment-associated long-term morbidity [5, 6, 25]. For patients inoperable or with a moderate or high surgical risk associated with the nerves and/or vascular structures, we recommend limited surgical removal and postoperative RT to balance the incidence associated with optimal tumor control and treatment.

In recent years, with the increasing application of PBT in children with central nervous system tumors, encouraging clinical results have been reported. Some radiation oncologists believe that PBT may become the radiotherapy strategy of choice for craniopharyngiomas in the future [26, 27]. In our systematic review, the

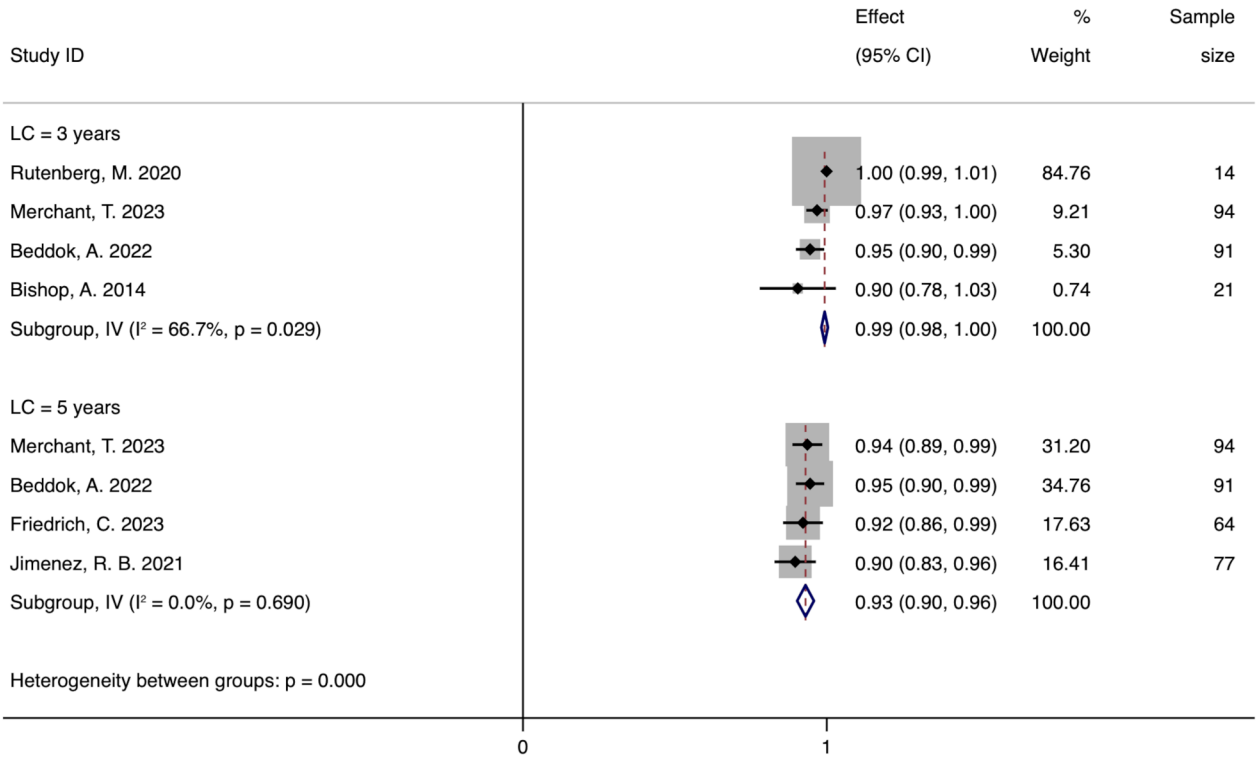

Fig.2 The pooled incidences of LC after PBT for craniopharyngiomas

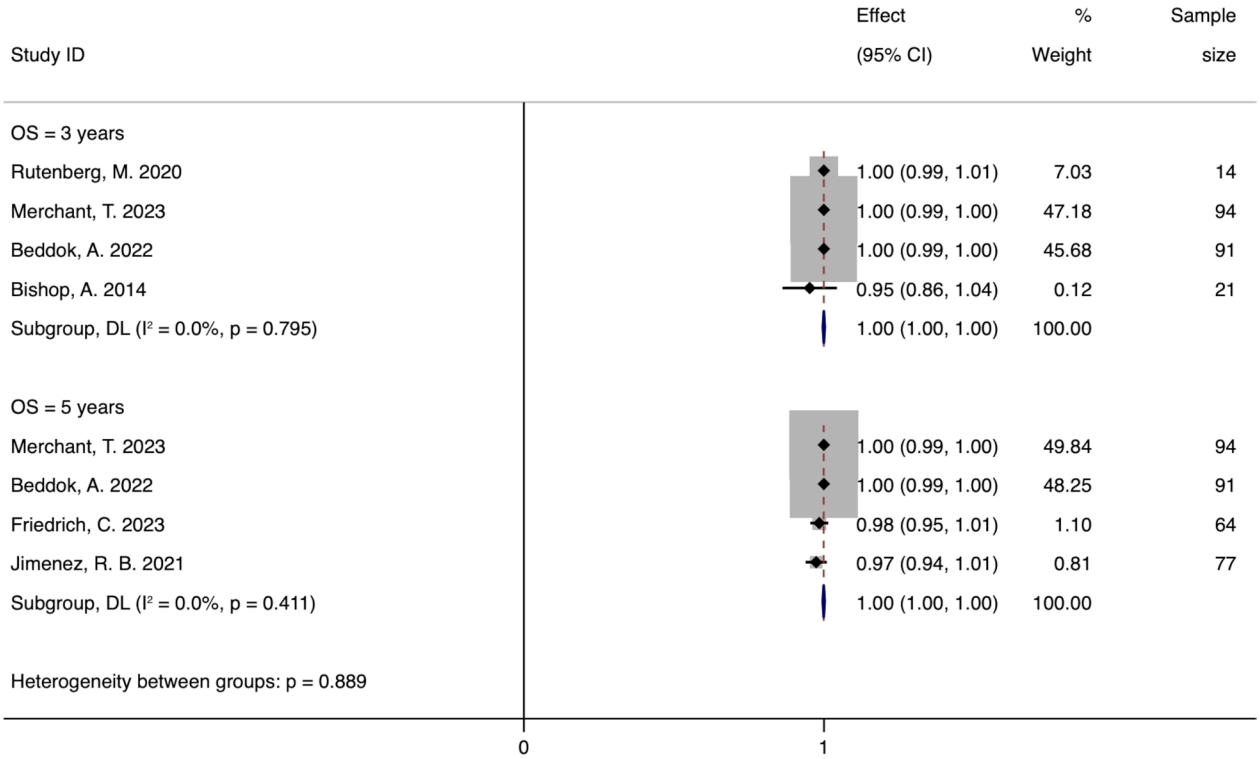

Fig.3 The pooled incidences of OS after PBT for craniopharyngiomas

meta-analysis revealed that the LC rates at 3 and 5 years were 99% and 93%, respectively (Fig. 2). After 3 and 5 years of PBT, the OS rates for craniopharyngiomas were 100% and 100%, respectively (Fig. 3). PBT is currently performed in only a few clinical centers, whereas XRT is conducted in many clinical institutions. However, whether PBT for craniopharyngioma can improve survival outcomes compared with conventional photon RT remains an interesting question. Merchant et al. compared the clinical outcomes of PBT and XRT for craniopharyngioma. They found that the survival associated with PBT was slightly better than that associated with XRT; however, the difference was not significant [17]. The study included 94 patients with craniopharyngiomas treated with PBT, with 3-year and 5-year progression-free survival (PFS) of 96.8% (95% CI: 90.4–99.0) and 93.6% (86.3–97.1), respectively; and 101 patients treated with XRT, with 3-year and 5-year PFS of 96.0% (95% CI: 89.7–98.5) and 90.0% (82.2–94.5), respectively [17]. Similarly, Friedrich et al. obtained similar results [21]. Ninety-nine patients with craniopharyngioma were enrolled in the study, 64 of whom received PBT and 35 received XRT. The 5-year event-free survival (EFS) rates after PBT and XRT were comparable (92% ± 4% vs. 91% ± 4%, $p = 0.42$) [21]. Bishop et al. compared the clinical outcomes of PBT and XRT for craniopharyngioma. They found that the survival associated with XRT was slightly better than that associated with PBT; however, the difference was not significant [15]. Fifty-two patients with craniopharyngioma were enrolled in the study, 21 of whom underwent PBT, and 31 underwent XRT. The 3-year nodular failure-free survival (NFFS) rates after PBT or XRT were comparable (91.7% vs. 96.4%, $p = 0.546$). Moreover, the 3-year OS rates after PBT or XRT were comparable (94.1% vs. 96.8%, $p = 0.742$) [15]. These results suggest that PBT does not affect survival outcomes for craniopharyngioma compared with XRT. However, the utilization of both radiation techniques differed over time, with PBT being more predominant at the end of the inclusion period. Therefore, a bias through other evolving techniques in XRT cannot be excluded [21]. In addition, this was only a 5-year follow-up study, and results of follow-ups of 10 years or more need to be determined in the future.

Regarding the median total dose of PBT for craniopharyngioma, the initial results were relatively conservative at 50.4 Gy (RBE) (Table 4) [15]. In recent years, as reported by several research centers, the median total dose was mostly 54 Gy (RBE), and the most common fraction dose was 1.8 Gy (RBE) (Table 4) [17–22]. To our knowledge, there are two different clinicopathological variations of craniopharyngiomas: classic adamantinomatous and papillary subtypes [28]. The papillary subtype occurs predominantly in adult patients, accounting for about 14–50% of tumors in this age group [6, 28]. Calcification is rare in this histopathological type, and tumor boundaries are usually marked, with less peripherally invasive growth than in the adamantinomatous type [29]. Based on the differences in the clinical treatment and clinical outcomes of craniopharyngiomas in children and adults [29], the dose pattern of PBT should be further explored in future studies. Individualized PBT for craniopharyngiomas is a problem worth discussing further.

In our systematic review, acute and late toxicities after PBT for craniopharyngiomas were mainly grades 1 and 2, respectively (Table 4) [15–22]. Acute toxicity grade 3 (including blood and lymphatic system disorders) was observed in two studiesy, and the incidence rate was 1–4% [17, 19]. Late toxicity grade 3 (fatigue, headaches, vision disorders, weight gain, vascular disorders, endocrine disorders, nervous system disorders, psychiatric disorders, and others) was observed in two articles, with an incidence of 6–6.3% [17, 22]. Moreover, grade 4 late toxicity (hypernatremia, eye disorders, sepsis, and hyponatremia) was observed in one study, with an incidence of 2% [17].

Compared to conventional XRT, PBT has superior radiophysical properties [9–11]. It can deposit the majority of the dose in the "Bragg peak" region, providing a more favorable dose distribution than photons [9–11]. The expected benefit of PBT in patients with craniopharyngioma may be attributed primarily to the reduction in the integral dose around the normal brain tissue, which is specific to PBT. A dosimetric comparison between PBT and XRT treatment regimens in children with craniopharyngioma showed that PBT was administered at lower doses to important structures, such as the hippocampus, subventricular area, and vascular system [10]. In addition, Merchant et al. (2008) revealed that PBT may help lower the irradiation dose to the temporal lobe and cochlea, reducing the risk of cognitive ability and hearing loss [30]. However, another dosimetric comparison of the treatment plans demonstrated no relevant differences in radiation doses to the hypothalamus or pituitary gland between PBT and XRT [21].

Merchant et al. analyzed the toxicities associated with PBT and XRT in craniopharyngiomas. PBT did not show significant improvement in hypothalamic- or pituitary-related toxicity compared to XRT. However, improvements in cognitive function in children may be one of its advantages [17]. Studies have shown that the main benefit of PBT for craniopharyngioma is improved neurocognitive function [31]. Toussaint et al. compared the cognitive test results from two prospective trials in 2017, including PBT (NCT01419067) and XRT (NCT00187226), for craniopharyngiomas in children [32]. When the normal brain radiation dose distribution was analyzed, the

academic achievement scores (reading and math) for craniopharyngioma did not change significantly after PBT, whereas patients treated with XRT showed a significant decline [32]. It is worth noting that the relationship between dose restriction in the temporal lobe and hippocampus and memory decline is still debated [33–35]. Based on Gondi et al.'s study, hippocampal dose restriction (D40% < 7.3 Gy) may be associated with the preservation of memory and quality of life [35, 40].

In our systematic review, five studies reported the cystic dynamics of craniopharyngiomas (Table 4) [15, 17–20], which may be related to treatment replanning, toxicity, and prognosis. Studies have shown that after XRT for craniopharyngioma in children, the cyst/tumor expansion rate is approximately 11–64% [9, 37]. In Winkfield's study involving 17 children with craniopharyngiomas, six (35%) developed significant cystic changes during PBT, including one patient who required a modified treatment plan [38]. Merchant et al. reported 14 cases of children with craniopharyngiomas who developed cyst growth during PBT treatment. Eight patients required replanning, four required cyst drainage, and two required replanning and drainage [17]. Ajithkumar et al. reported five cyst growths during PBT treatment, in which two patients required replanning and cyst drainage [20]. In addition, studies by Bishop and Rutenberg et al. reported cyst growth during PBT, with some patients requiring replanning [15, 18]. Notably, cyst shrinkage occurs during RT, and revision of the RT plan may be necessary [15]. Evidence suggests that cyst enlargement may occur after RT. Early cyst expansion rates have been reported to be 40–60% within 6 months of RT completion [15, 37, 39, 40]. Fortunately, craniopharyngioma cyst growth after RT is usually transient, and if the patient remains asymptomatic, most cases require only close clinical and radiographic follow-up without surgical intervention [37, 39, 40]. One study revealed a lower rate of cyst change during and after PBT compared to photons [15]. However, it is unclear whether there is a difference in cyst dynamics during or after RT (protons or photons) for craniopharyngiomas of different ages (adult or pediatric) or histologic subtypes (adamantinomatous or papillary).

As an advantageous RT technique, PBT has shown promising efficacy and acceptable toxicity in the treatment of craniopharyngioma. However, some aspects of this systematic review and meta-analysis remain insufficient. First, gray literature was not included, and the results may have led to publication bias. Second, the eightstudies originated from three countries (62.5% from the USA, 25% from the UK, and 12.5% from France); therefore, our results may have been biased. Third, craniopharyngioma is a rare disease with histological types, including the classic adamantinomatous and papillary subtypes, and randomized studies are difficult to perform. Based on the differences in clinical treatment and clinical outcomes regarding craniopharyngiomas between children and adults, different types of craniopharyngiomas may have inconsistent optimal dose patterns, and individualized PBT requires further investigation. Fourth, the relative additional costs of PBT compared to photon RT, including healthcare environment, socioeconomic status [41], and access to technology, are substantial and influence the generalizability of some of the findings. Fifth, the included articles were retrospective studies with small sample sizes; in particular, some of the toxicity results may have been speculative. Craniopharyngiomas are classified as WHO grade I neoplasms, and long-term survival can be achieved regardless of surgery or combined RT. In our systematic review, the follow-up period of the included studies was relatively short, limiting the reliability of the long-term survival and toxicity assessments regarding PBT for craniopharyngiomas. Notably, in children and adolescents with craniopharyngiomas, tumor recurrence, cyst dynamics, quality of life (QoL), cognitive ability, frontal lobe encephalomalacia, hypothalamic and pituitary dysfunction, optic neuropathy, growth and development, and secondary cancer should be assessed/monitored throughout the growth and development cycles. Increasing the number of patients and extending follow-up to assess long-term outcomes are the goals of future studies on craniopharyngioma survivors. Finally, whether PBT is superior to other RT technologies must be determined through high-quality prospective randomized controlled clinical trials in patients with craniopharyngiomas.

Conclusion

PBT for craniopharyngiomas, especially in children and adolescents, has shown encouraging survival results and appears to have no current evidence of superiority over conventional photon RT.The safety and efficacy of PBT for craniopharyngioma must be determined through high-quality prospective randomized controlled clinical trials.

Abbreviations

PBT	Proton beam therapy
LC	Local control
CI	Confidence interval
OS	Overall survival
WHO	World Health Organization
GTR	Gross tumor resection
STR	Sub-total resection
RT	Radiotherapy
XTR	X-rays radiotherapy
JBI	Joanna Briggs Institute
Cis	Confidence intervals
SEER	Surveillance Epidemiology and End Results
OR	Odds ratio
PFS	Progression-free survival

EFS Event-free survival
NFFS Nodular failure-free survival
QoL Quality of life

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