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Emerging Outcome Trends From Proton Therapy for Pediatric CNS Tumors: A Systematic Review

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ABSTRACT

Purpose: This systematic review aims to provide a summary of outcomes of pediatric brain tumor patients treated with proton therapy (PT). Outcomes focused on include long-term efficacy and late toxicities. This study provides an analysis of survival, disease control, and safety outcomes across major pediatric brain tumor histologies to support contemporary clinical decision-making.

Methods: A literature search was conducted across PubMed, Scopus, and Web of Science to identify studies reporting overall survival (OS), progression-free survival (PFS), local control (LC), or late toxicity in patients under 21 years with brain tumors treated with PT. Weighted linear regression was performed on survival outcomes modeling trends over post-treatment follow-up. Safety outcomes were qualitatively assessed based on histology and pooled where possible to facilitate cross-study comparison.

Results: Seventy-seven studies were included, with 40 reporting on OS following PT in a total of 3798 patients. Statistically significant time-dependent models were obtained for medulloblastoma (PFS: $P = .0018$), ependymoma (OS: $P = .0002$, PFS: $P = .0006$, LC: $P = .001$), base of skull (BOS) chordoma (OS: $P = .0498$), and the mixed histology group (OS: $P = .028$), with trends observed in other histologies. LGG and craniopharyngioma demonstrated high survival, showing over 95% OS up to 10 years after treatment. Toxicity outcomes revealed common late toxicities, including endocrinopathies (ranging from 11.7% in ependymoma to 94% in craniopharyngioma), vasculopathy (1%: LGG - 36%: craniopharyngioma), hearing loss (4%: ependymoma - 26.3%: medulloblastoma), and neurocognitive decline (no significant decline: LGG - 1.5 points annual decline: medulloblastoma), with wide variations in incidence across histology reflecting differences in tumor location and treatment burden.

Conclusion: Statistically significant trends in medulloblastoma, ependymoma, and BOS chordoma were identified, along with consistent outcomes in LGG and craniopharyngioma outcomes. Together, these findings provide clinicians with clearer expectations of prognosis following PT and establish reference benchmarks that can inform treatment planning, counsel families, and serve as a comparative foundation for future clinical research.

Introduction

Among the pediatric population, brain tumors are the most common solid malignancies and represent the leading cause of cancer-related deaths.[1] Advances in surgery, chemotherapy, and radiotherapy (RT) have progressively improved survival outcomes; however, they may lead to long-term morbidity. Especially in the case of cranial RT, late side effects such as neurocognitive impairments, endocrine dysfunction, hearing loss, and secondary malignancies may arise, which are especially concerning in the pediatric population,[2] given their longer life expectancy and heightened vulnerability to treatment-related toxicity.

Proton therapy (PT) has been shown to lower the incidence and severity of long-term toxicities and to improve quality of life (QoL) for childhood brain cancer survivors compared to photon-RT.[3,4] Emerging dosimetric studies further support these findings by demonstrating reduced integral dose to healthy pediatric tissue.[5] Ongoing research,

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along with economic and technological advancements, will be essential in defining the long-term clinical and cost-effectiveness of PT in pediatric neuro-oncology.

Recent systematic reviews in this field have focused on a single tumor type or a single type of toxicity. Some of these include Baqai et al (2023)[6] and Doig et al (2022)[7] analyzing QoL; Bavle et al (2021)[8] examining vasculopathy; Elkatatny et al (2023)[9] investigating moyamoya syndrome; Lassaletta et al (2023)[10] and Yahya et al (2021)[11] evaluating neurocognitive outcomes; Uphadyay et al (2022)[12] exploring secondary malignancies; and Young et al (2023)[13] assessing medulloblastoma. A common point among these reviews was the limited pool of data available for analysis. Systematic reviews that collate information spanning specific tumor types and outcomes are lacking. As such, there is a timely need for an up-to-date systematic synthesis of the current clinical data regarding PT for pediatric brain tumors.

A systematic review was undertaken with a specific focus on the outcomes of PT for pediatric brain tumors. Published evidence on overall survival (OS), progression-free survival (PFS), local control (LC), and late toxicities in pediatric patients following cranial PT for the most prevalent diseases for which PT is considered an option was analyzed and summarized. Patterns or limitations in the available evidence were aimed to be identified, along with providing the largest and most current synthesis of PT outcomes for pediatric brain tumors to date. Unlike prior systematic reviews, this review applies longitudinal trend modeling of survival outcomes as a function of post-treatment follow-up and synthesizes outcomes across multiple tumor histologies, offering a novel descriptive perspective on how disease control evolves over time after PT. This integrated cross-histology and time-trend approach provides a broader and more unified clinical context than has previously been available. Ultimately, the goal is to provide clinicians with evidence-based insights that inform treatment decision-making and facilitate strategic planning for future research initiatives, particularly as PT becomes increasingly accessible globally.

Methodology

Study design and registration

This systematic review followed the PRISMA guidelines[14] and was registered with PROSPERO (ID: CRD42024599646), ensuring methodological transparency and reproducibility.[15]

Eligibility criteria

Included studies were those that reported on pediatric patients (defined as < 21 years of age) with primary intracranial tumors treated with PT. Eligible studies needed to report at least 1 survival outcome (such as OS, PFS, or LC) or 1 safety outcome (such as treatment-related toxicities or late adverse effects) to ensure inclusion of clinically meaningful data.

Literature search and study selection

PubMed, Scopus, and Web of Science were searched up to December 2024 using terms for “pediatric,” “PT,” and brain tumor types. A representative search string was: (“PT” OR “proton RT”) AND (“pediatric” OR “pediatric” OR “child*”) AND (“brain tumor” OR “glioma” OR “craniopharyngioma” OR “medulloblastoma” OR “ependymoma” OR “chordoma”). Reference lists of relevant papers and reviews were screened. Titles and abstracts were assessed, duplicates removed, and full texts reviewed against the following criteria:

Inclusion criteria:

- Population: Pediatric patients, defined as younger than 21 years old, diagnosed with primary brain or BOS tumors.
- Intervention: RT delivered specifically through PT.
- Outcomes: Studies must report on clinical outcomes, including OS, PFS, event-free survival, LC, or data concerning late treatment-related toxicities.
- Study designs: Prospective or retrospective observational cohort studies and clinical trials.
- Publication timeframe: No publication date restrictions were applied to maximize capture of available PT data.

Exclusion criteria:

- Case reports, narrative reviews, editorials, and commentaries.
- Preclinical or animal studies.
- Studies without separate reporting for pediatric cohorts.
- Publications lacking clear outcome data.

Data extraction

Data were extracted into a structured spreadsheet, including the following variables: study characteristics (author and year), patient demographics (sample size, age, gender, and histology), treatment details (PT technique, dose, and fractionation), outcomes (OS, PFS, LC, and late toxicities), and follow-up duration. Data extraction was performed in duplicate to minimize transcription errors.

Data synthesis and analysis

Survival outcomes were summarized qualitatively and modeled using weighted linear regression (weights by cohort size irrespective of study type) via Real Statistics in Excel. Since individual patient time-to-event data were unavailable, weighted linear regression was used as a descriptive method to visualize aggregate survival trends. This approach does not account for censoring and should be interpreted as illustrative for general trends rather than precise survival modeling. Toxicity incidences were pooled when comparable; otherwise, results were synthesized narratively due to variability in reporting and heterogeneity across tumor types. Analyses were restricted to PT as most studies lacked photon-treated comparators.

Bias assessment

Study quality was assessed using the Newcastle-Ottawa Scale (NOS), covering 3 domains: Selection (0-4), Comparability (0-2), and Outcome (0-3). Total scores (0-9) classified the risk of bias as high (0-3), moderate (4-6), or low (7-9), consistent with accepted standards for observational study appraisal.

Results

PRISMA flow diagram and study selection outcomes

Figure 1 displays a PRISMA flow diagram. The initial database search yielded a total of 1022 unique studies. Of these, 182 were found eligible for inclusion based on the screening of the title and abstract. Secondary screening of the full texts resulted in 121 articles being excluded due to various reasons such as lack of reported outcomes, non-separation of pediatric cohorts or treatment being for recurrent rather than primary tumors. These exclusion criteria are consistent with evidence-synthesis standards to avoid bias introduced by mixed or recurrent-disease cohorts. The remaining 61 articles increased to 77 following the inclusion of an additional 16 articles that appeared in references or systematic reviews.

Summary of included studies

The total number of included studies for analysis was 77 (59 retrospective, 15 prospective, and 3 systematic reviews), with 40 (52%) describing efficacy outcomes, 53 (69%) describing safety outcomes, and

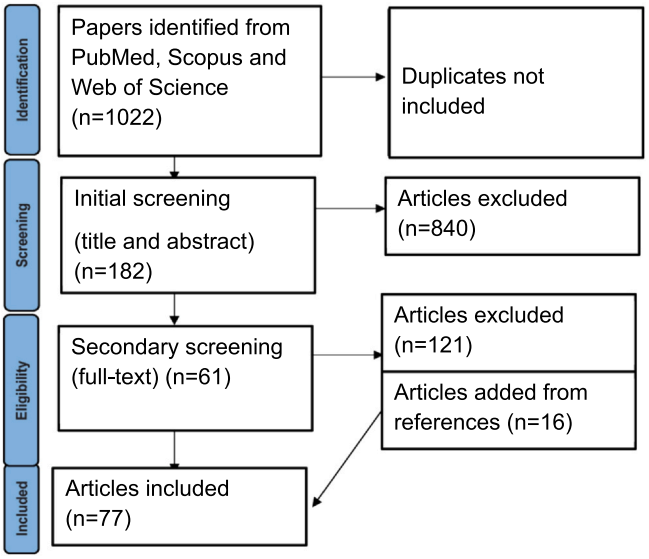

Figure 1. PRISMA flow diagram clearly illustrating each step of study selection. Articles were excluded for not meeting eligibility criteria.

16 (21%) of these papers including data for both efficacy and safety. Only data from original primary cohorts were extracted from the systematic reviews, ensuring that no double-counting took place.

The 77 included papers accounted for a total of 7294 patients, with the majority from the mixed histology subset. The number of patients with documented survival outcomes for PT was 3798.

Summary of bias assessment

Appendix Figure A.3.2 shows the distribution of the NOS score across the 77 included studies. The mean NOS score was 7.87, indicating overall high quality. Thirty-four (44%) studies received a score of 9 (the maximum), 16 (21%) received an 8, 12 (16%) received a 7, 14 (18%) received a 6, none received a 5, and 1 (1%) received a 4. This shows that the vast majority (81%) of included studies were at a low risk of bias, and the remaining (19%) were of only moderate risk of bias. The full list of bias assessment outcomes can be found in the appendix.

Outcomes by tumor histology

This section presents the pooled outcome data extracted from the included studies. The outcomes are grouped based on histology and include OS, PFS, and LC where sufficient data were available. The late toxicity and safety data are also presented within each tumor-type subheading. Considerable heterogeneity exists between studies regarding tumor histology, surgical extent, chemotherapy use, focal versus craniospinal radiation, treatment era, and toxicity definitions. As such, pooled trends should be interpreted cautiously and as descriptive rather than directly comparable estimates.

The full tables of included studies and linear regression outputs (including parameter confidence intervals and p values) can be found in Appendix Figure A.1.

Low-grade glioma (LGG)

Figure 2 summarizes the LGG results, which did not yield statistically significant trends.

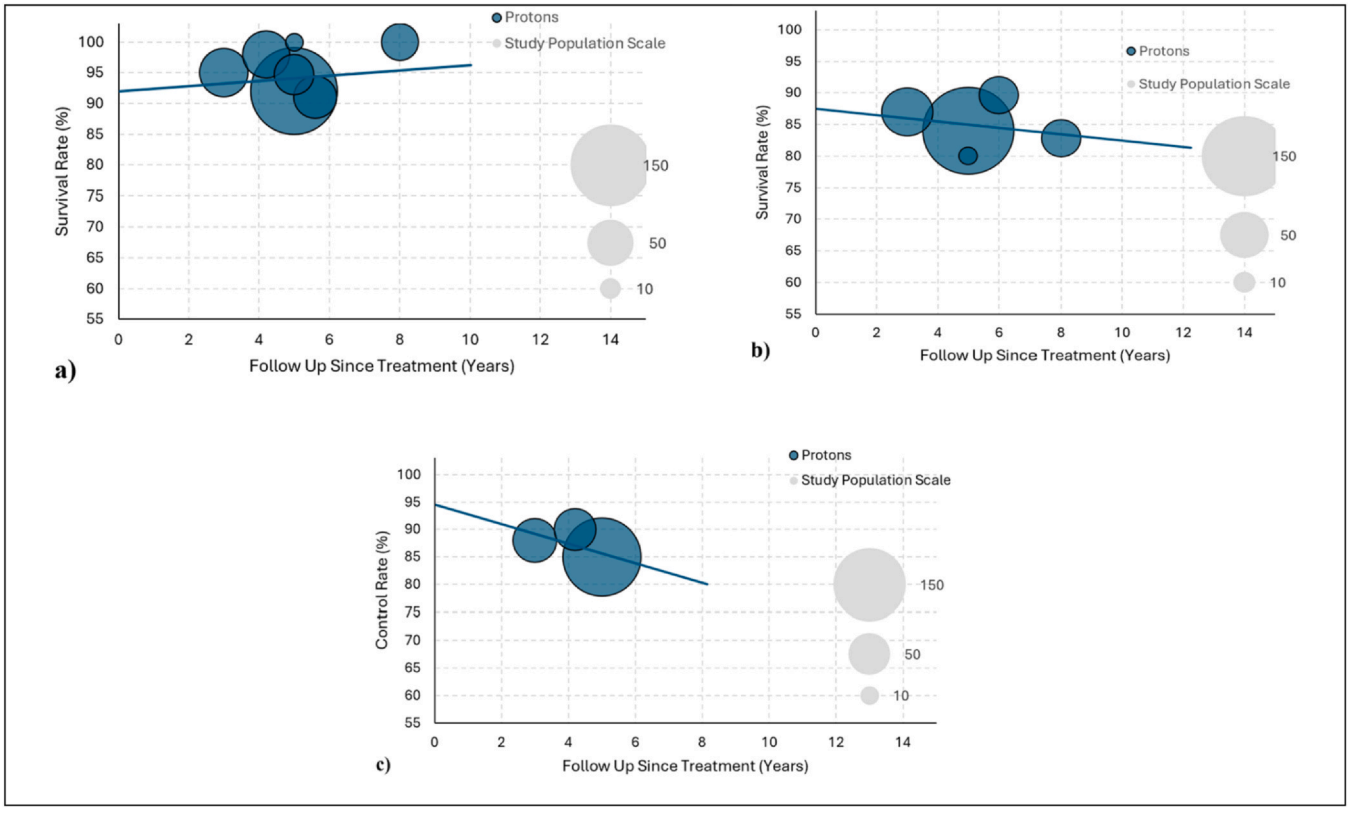

Figure 2. Low-grade glioma (LGG) studies modeled as dependent on median follow-up time since treatment in years (t). Bubble size represents the number of patients in the study. Linear trend shows the results of weighted linear regression of the data. (a) It shows the results of overall survival (OS) for 7 included studies totaling 397 patients. The weighted linear regression did not yield statistical significance and is modeled as: OS(%) = 92.03 + 0.42 t. (b) It shows the results of progression-free survival (PFS) for 5 included studies totaling 299 patients. The weighted linear regression did not yield statistical significance and is modeled as: PFS (%) = 87.54-0.52 t. (c) It shows the results of local control (LC) for 3 included studies totaling 279 patients. The weighted linear regression did not yield statistical significance and is modeled as: LC(%) = 94.56-1.81 t.

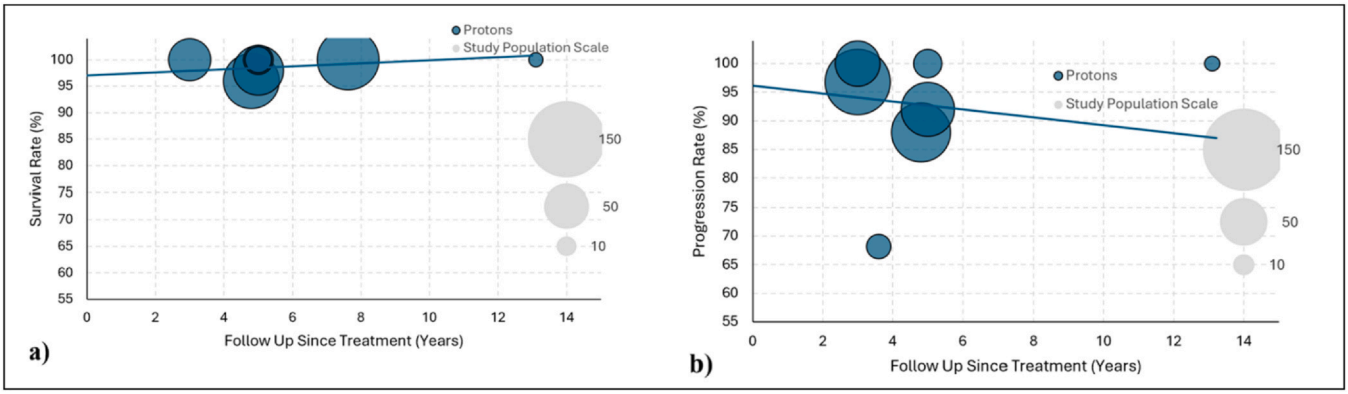

Figure 3. Craniopharyngioma studies modeled as dependent on median follow-up time since treatment in years (t). Bubble size represents the number of patients in the study. Linear trend shows the results of weighted linear regression of the data. (a) It shows the results of overall survival (OS) for 7 included studies totaling 325 patients. The weighted linear regression did not yield statistical significance and is modeled as: OS(%) = 97.05 + 0.29 t. (b) It shows the results of progression-free survival (PFS) for 7 included studies totaling 316 patients. The weighted linear regression did not yield statistical significance and is modeled as: PFS (%) = 96.12–0.71 t.

Ludmir et al (2019)[16] noted a higher frequency of pseudo-progression from PT vs photon-RT (45% vs 25%, HR = 2.15, 95% CI: 1.06-4.38, P = .048, n = 51). Stock et al (2022)[17] reported 11/20 cases of pseudo-progression, typically arising after 6.5 months and lasting 7.4 months. Pseudo-progression is not linked to long-term morbidity; however, its high incidence and imaging confusion require clinical awareness.

Late toxicity and safety outcomes

For pediatric LGG, there were 7 studies reporting toxicity follow-up from 2 to > 8 years. Overall safety was favorable, with only a few severe events.

Three studies showed stable neurocognitive outcomes. Greenberger et al (2014)[18] found no significant (P = .8) decline in full-scale intelligence quotient (FSIQ) over 7.6 years with 32 patients. Heitzer et al (2021)[19] reported preserved cognition across 18 patients with 2-9 years follow-up. Badiyan et al (2021)[20] observed stable QoL scores 2 years after treatment (65.63 ± 30.71 baseline vs 64.81 ± 21.15 follow-up); however, large uncertainty limits interpretation.

Visual toxicity was among the most common adverse effects for LGG patients. Greenberger et al (2014)[18] reported that 83.3% of patients remained visually stable after 7.6 years. Hanania et al (2021)[21] reported a 40% rate of legal blindness in patients treated with combined chemotherapy and PT, compared with a 0% rate for patients who received upfront PT.

Indelicato et al (2019)[22] investigated 174 patients, finding 22% new-onset hormone deficiency and 2 cases each of brainstem necrosis and vasculopathy. Visual and endocrine deficiencies were not uniformly reported but appear to be among the most common toxicities.

Craniopharyngioma

Figure 3 summarizes the results for craniopharyngioma cohorts; statistical significance was not achieved across OS or PFS, and LC results were not present in selected studies.

Late toxicity and safety outcomes

Five studies documented late effects in pediatric craniopharyngioma, with median follow-up ranging from 3 to 7.6 years. These outcomes focused mostly on endocrine, visual, and vascular complications.

Jimenez et al (2021)[23] found that 94% of 77 patients required hormone replacement up to 5 years post-treatment. Aldave et al (2023)[24] reported 68% pituitary dysfunction, 64% hypothalamic obesity, and 55% diabetes insipidus.

Merchant et al (2023)[25] reported vision impairment in 7% of 54 patients after 5 years, whereas Jimenez et al (2021)[23] observed a higher rate of 40%. In most cases, PT had the ability to spare the optic pathways during craniopharyngioma treatment.

Lucas et al (2022)[26] documented 36% of 94 patients with vascular abnormalities (including stenosis, aneurysm, and dilated perivascular spaces). Cumulative incidences of these abnormalities were: grade 1 = 41.8%, grade 2 = 18.3%, grade 3 = 5.9%. Merchant et al (2023)[25] also reported severe vasculopathy in 4% of patients and observed 2 cases of radiation necrosis and 3 cases of permanent neurological deficits. This study saw a total of 17 cases of grade 3-4 toxicity among the 94 patients, including headaches (n = 6), seizures (n = 5), and vascular disorders (n = 6).

By contrast, Young et al (2022)[27] reported no grade ≥3 late toxicities, nor neurocognitive decline or hearing loss after 5 years, though this likely reflects the small sample size of 8 patients.

Overall, PT for craniopharyngioma offers strong disease control, but high rates of endocrine and vascular late effects remain concerning, warranting hypothalamic sparing strategies during treatment planning and long-term follow-up.

Medulloblastoma

Figure 4 summarizes the medulloblastoma studies.

Most included studies predate the now-dominant prognostic determinant of molecular subgrouping, this limitation should be considered when interpreting outcomes.

No included medulloblastoma studies reported on LC.

Late toxicity and safety outcomes

Reported late toxicities for pediatric medulloblastoma most frequently focused on auditory, endocrine, neurocognitive, and vascular effects.

The Ontario HTA study (2021)[28] observed 26.3% grade 3 hearing loss and 2.6% grade 4 hearing loss across 84 patients (median follow-up of 56 months). Jimenez et al (2013)[29] reported 2 of 14 patients requiring hearing aids, and Yock et al (2016)[30] noted ototoxicity rates of 12% and 16% after 3 and 5 years, respectively (59 patients).

The Ontario report[28] also described 19% hypothyroidism and, in a separate cohort of 77 patients with a 70 months follow-up, 22.5% hypothyroidism. Aldrich et al (2021)[31] found that 63% of 64 patients required hormone replacement after median follow-up of 5.6 years, including 16.7% hypothyroidism and 13.3% adrenal insufficiency. Yock et al (2016)[30] reported 27%, 55%, and 63% hormone deficiency, with the majority being growth after 3, 5, and 7 years respectively.

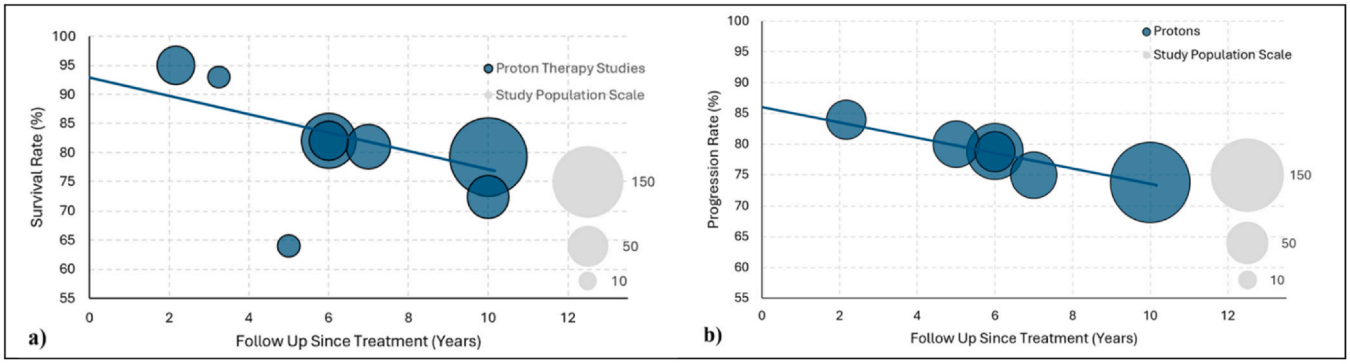

Figure 4. Medulloblastoma studies modeled as dependent on median follow-up time since treatment in years (t). Bubble size represents the number of patients in the study. Linear trend shows the results of weighted linear regression of the data. (a) It shows the results of overall survival (OS) for eight included studies totaling 494 patients. The weighted linear regression did not yield statistical significance and is modeled as: OS(%) = 92.96–1.61 t. (b) It shows the results of progression-free survival (PFS) for 7 included studies totaling 316 patients. The weighted linear regression yielded statistically significant results (P = 0.002) and is modeled as: PFS (%) = 86.15–1.27 t.

Eaton et al (2021)[32] reported a mean FSIQ of 99.6 at 5.3 years post PT (n = 17), significantly higher than patients treated with photon-RT (mean 86.2, P = .021). Kahalley et al (2020)[33] reported a significant decline of global IQ (0.9 points per year) for patients treated with photon-RT, while patients receiving PT showed a non-significant decline, consistent with findings from Jimenez et al (2013).[29] Yock et al (2016)[30] found a mean FSIQ decline of 1.5 points per year for 54 patients treated with PT. As Eaton (2021) reported absolute FSIQ scores rather than longitudinal change, the direct comparative impact between photon-RT and PT cohorts remains uncertain.

Trybula et al (2021)[34] reported 42 cavernomas among 49 patients, with only 3.3% remaining cavernoma-free at 5 years. Kamran et al (2018)[35] recorded 30% incidence of posterior fossa syndrome (116 patients with median 5-year follow-up). In their study, HRQoL assessments demonstrated annual improvement (child self-report +1.8, parent-proxy +2.0), patients with posterior fossa syndrome scored significantly lower (child: 69.5 vs 56; parent: 63.3 vs 49.7).

Yock et al (2016)[30] documented acute toxicities (grade 3 = 37 and grade 4 = 12) and late toxicities (grade 3 = 7 and grade 4 = 1) among 59 patients. Ruggi et al (2022)[36] reported 7 of 43 patients with acute grade 3 toxicity and 2 late events: grade 3 RBC transfusion and grade 4 CMV encephalitis.

PT for pediatric medulloblastoma continues to show auditory and endocrine dysfunction, and vascular effects represent significant late toxicities requiring long-term monitoring.

Ependymoma

Figure 5 summarizes findings for ependymoma, which showed one of the steeper declines in efficacy outcomes with time among the considered tumor types.

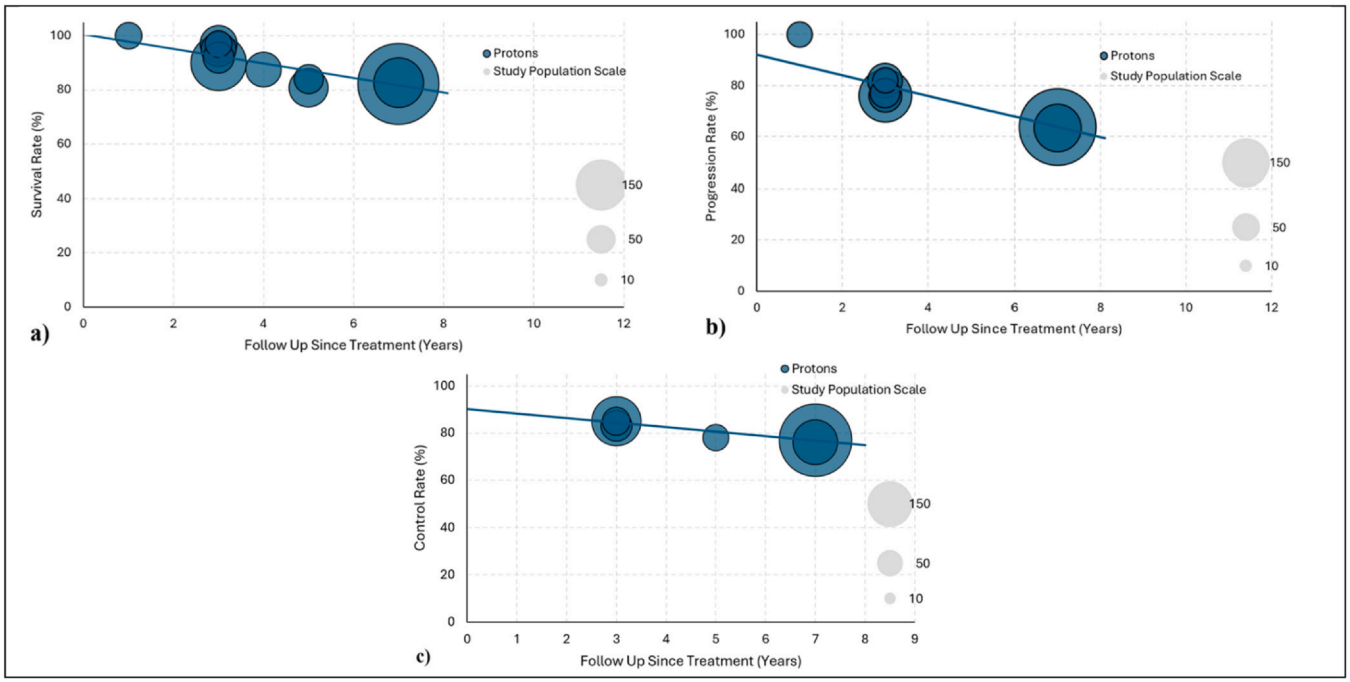

Figure 5. Ependymoma studies modeled as dependent on median follow-up time since treatment in years (t). Bubble size represents the number of patients in the study. Linear trend shows the results of weighted linear regression of the data. (a) Figure 5-a shows the results of overall survival (OS) for eleven included studies totaling 1209 patients. The weighted linear regression yielded statistically significant results (P = .0002) and is modeled as: OS(%) = 100.4–2.7 t. (b) It shows the results of progression-free survival (PFS) for eight included studies totaling 999 patients. The weighted linear regression yielded statistically significant results (P = 0.0006) and is modeled as: PFS(%) = 91.9 – 4.1 t. (c) It shows the results of local control (LC) for 6 included studies totaling 887 patients. The weighted linear regression yielded statistically significant results (P = .001) and is modeled as: LC(%) = 90.1–1.93 t.

Similar to the prior section, molecular subgrouping was not widely utilized by included studies. Seeing as this is a dominant prognostic factor for these tumors, this limitation should be considered when interpreting trends.

Weighted linear regression on the OS, PFS, and LC results all produced a statistically significant trend ($P = .0002$, $P = .0006$, $P = .001$, respectively). It can be expected that, at least within the first 7 years post PT, the efficacy outcomes for pediatric ependymoma follow the linear models stated in Figure 5.

Late toxicity and safety outcomes

Late toxicity outcomes following PT for pediatric ependymoma demonstrate a pattern of endocrine, auditory, and neurological complications. Four included studies provide detailed observation on these toxicities.

Indelicato et al (2021)[37] reported that 45 of 386 patients (11.7%) required hormone replacement therapy within 5 years post-treatment, with growth hormone representing 38 of those cases. Ares et al (2016)[38] found endocrine complications in 6 patients out of 50, with 3 being growth hormone deficiency and 3 being hypothyroidism after a mean follow-up of 43 months.

Indelicato et al (2021)[37] also reported 5.4% of their patients requiring hearing aids after 5 years, while Ares et al (2016)[38] noted 2 cases (4%) of grade ≥3 deafness.

The most serious complications for ependymoma patients appeared to be brainstem injury and radiation-induced necrosis. With an initial cohort of 79, the Ontario HTA (2021)[28] reported 7.3% necrosis after a median follow-up of 31 months. Sato et al (2017)[39] observed necrosis-related vasculopathy in 3 of 41 patients. Indelicato (2021)[37] reported grade ≥2 brainstem necrosis in 4% of cases and 2 necrosis-related deaths.

Ares et al (2016)[38] reported an overall 38% of patients experiencing grade 1 or 2 late toxicities, suggesting the majority of complications are of mild to moderate severity.

Base of skull (BOS) chordoma

Figure 6 summarizes BOS chordoma study results.

No included studies reported on PFS or late toxicities.

Discussion

Interpretations outcomes by tumor type

Low-grade glioma

The results for LGG reaffirm its favorable prognosis. Across 7 PT studies (397 patients), OS consistently exceeded 91% up to 8 years. Although regression did not reach significance ($P = .70$), the near-ceiling survival rates likely account for this. PFS also remained strong, between 87% and 90% at 3 years, with a gradual decline to ~83% by 8-12 years. LC data were more variable but suggested rates of approximately 85%-90% within 5 years. Toxicities were generally mild, including hormone deficiencies, occasional vasculopathy or radiation necrosis, and variable visual outcomes involving the optic pathways. Cognitive outcomes were largely stable.[16,18,19,21,22] PT therefore remains well-tolerated and highly effective for pediatric LGG, offering the additional advantage of reduced late toxicity in long-term survival, consistent with published dosimetric comparisons showing reduced integral dose to healthy tissue.[40]

Summary of late effects: Mostly mild toxicities. Neurocognition remained stable,[18,19] endocrine dysfunction ~22%,[22] visual outcomes varied,[21] pseudoprogression up to 45%.[16]

Craniopharyngioma

Craniopharyngioma presents challenges due to proximity to the hypothalamic–pituitary axis and optic chiasm. PT demonstrated excellent OS, with 5 of 7 studies reporting 100% survival up to 13 years; the remainder reported 96%-98%. PFS was generally high (> 88%) but variable, with 1 small study reporting as low as 68%. Longer follow-up remains limited, and regression was not significant ($P = .75$). No studies reported LC, reflecting the emphasis on recurrence and function over focal control. PT is therefore highly effective post-conservative surgery, but endocrine morbidity, hypothalamic obesity, and vascular complications such as moyamoya disease remain persistent burdens.[23,25,26]

Summary of late effects: High rates of hormone replacement (up to 94%), vision loss (≤40%), hypothalamic obesity (≤64%), and vascular sequelae.[23,25,26]

Medulloblastoma

Medulloblastoma is the most common malignant pediatric brain tumor and typically requires CSI. The reduced integral dose from PT relative to other techniques is especially attractive. Survival outcomes in this review are limited by the grouping of all subtypes together, despite molecular classification (eg, WNT, MYC-amplified) and extent of resection being major prognostic determinants. Eight included studies demonstrated OS starting near 95% at 2 years, declining to ~72%-79% by 10 years. One outlier study (Tran et al 2020[41]) reported poorer OS, likely due to younger patient age, higher WHO grade, and chemotherapy use. Regression nearly reached significance ($P = .07$), with most studies showing a steady 1.6% annual OS decline. PFS analysis (6 studies) showed highly consistent agreement, yielding a significant regression ($P = .0018$) of PFS (%) = 86.15–1.27 × years since

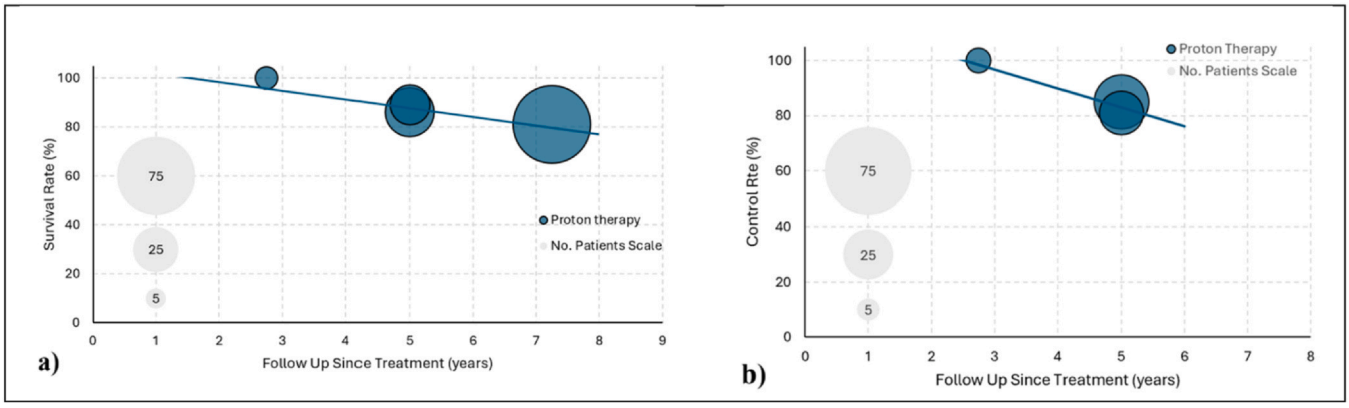

Figure 6. BOS chordoma studies modeled as dependent on median follow-up time since treatment in years (t). Bubble size represents the number of patients in the study. Linear trend shows the results of weighted linear regression of the data. (a) It shows the results of overall survival (OS) for 4 included studies totaling 127 patients. The weighted linear regression yielded statistically significant results (p = 0.049) and is modeled as: OS(%) = 105.1 – 3.37 t. (b) It shows the results of local control (LC) for 3 included studies totaling 54 patients. The weighted linear regression did not yield statistical significance and is modeled as: LC(%) = 120.3–7.37 t.

treatment. LC was not reported. Proton CSI therefore provides moderate long-term survival, with predictable temporal declines, highlighting the need for more durable systemic and risk-adapted strategies.

Summary of late effects: Highest burden of late effects, reflecting CSI. Growth hormone deficiency cumulative incidence 27%-63%[30]; ototoxicity 12%-26%[28–30]; posterior fossa syndrome in 30%.[35] Neurocognitive outcomes varied from stable[29,33] to a gradual annual IQ decline.[30] Grade ≥3 toxicities reached 14.5% across 297 patients.

Ependymoma

Ependymoma showed some of the steepest declines across tumor types. Survival outcomes are influenced by tumor location, resection extent, histological grade, and emerging molecular markers, which were not uniformly reported in the included studies. Eleven studies (1209 patients) demonstrated OS falling from 100% at 1 year to 80% at 7 years, with regression significant ($P = .0002$) and modeling a 2.7% annual decline. PFS analysis (8 studies, 999 patients) revealed a sharper drop, from 100% at 1 year to 63% by 7 years ($P = .0006$; 4.1% annual decline). LC data (6 studies, 887 patients) showed a more gradual but significant decline from 85% at 3 years to 77% at 7 years ($P = .001$). Outcomes remain suboptimal despite PT, underscoring the need for molecularly tailored approaches and more vigilant surveillance.

Summary of late effects: Endocrine dysfunction 11.7%-12%[37,38]; hearing loss ≤5.4%[37]; radiation necrosis 4%-7%,[28,37,39] with deaths in rare cases.[37]

BOS chordoma

There were few BOS chordoma studies (4 studies, 127 patients), but these indicated the steepest OS decline rate. Regression ($P = .0498$) modeled OS (%) = 105.1 – 3.37 × years since treatment over 2.75-7.25 years, reflecting anatomical challenges such as various chordoma subtypes (conventional, chondroid, dedifferentiated, and poorly differentiated) and radioresistance. LC (3 studies, 54 patients) declined to 81%-85% by 5 years but regression was not significant ($P = .22$), likely due to small samples. PT allows delivery of highly conformal doses with rapid dose fall-off, but long-term control remains difficult. The rarity of pediatric chordoma limits evidence, but current data support PT as the most appropriate modality.

Summary of late effects: Sparse data, but toxicity largely related to anatomical proximity of tumors to critical structures such as the brainstem.

Strengths and limitations

This review synthesizes outcomes from 90 studies and over 7000 patients, providing one of the most comprehensive evaluations of PT in pediatric brain tumors. However, limitations include reliance on retrospective cohorts, heterogeneity in surgical and adjuvant treatments, lack of molecular stratification, and limited follow-up durations. Along with the limitation of potentially inconsistent definitions of PFS and LC across studies, pose challenges for direct comparison and meta-analytic synthesis. The use of linear regression represents a descriptive simplification. Survival trajectories are influenced by censoring, which cannot be captured using this method; the results should therefore be interpreted strictly as visual summaries of aggregated trends rather than clinically predictive models. The preference for PT in pediatrics is largely related to the future malignancy risk, which requires decades of follow-up to quantify. Hence, the benefit in this space remains inferred rather than based on any hard clinical follow-up data.

Clinical implications and future directions

A recent analysis by Kiss-Miki et al 2025[42] showed no significant difference in 5-year OS between photon-RT and PT (OR = 0.80, 95% CI 0.51-1.23), but patients treated with photon-RT had markedly higher rates of hypothyroidism (up to 5-fold increased risk, OR = 0.22) and lower neurocognitive performance (mean IQ difference ~13 points). Accordingly, the main rationale for PT is not necessarily superior LC but the reduction of late effects due to integral doses, which may have substantial implications for long-term QoL.

In an era with expanding proton infrastructure and improved international communication, there appears to be an opportunity to establish prospective databases to collate and ultimately analyze long-term efficacy and outcome data. The current literature base appears to be largely retrospective, which carries associated bias, particularly regarding accurate scoring of toxicity, with inadequate median follow-up, particularly with regards to radiation-induced second malignancy risk.

Conclusion

This systematic review synthesizes efficacy and safety outcomes of PT for pediatric brain tumors across 5 histologies: LGG, craniopharyngioma, medulloblastoma, ependymoma, and chordoma. PT demonstrated consistently strong survival outcomes and favorable safety profiles, aligning with its theoretical dosimetric advantages.

Survival rates were excellent for LGG and craniopharyngioma, with most studies reporting over 95% survival up to 10 years. For more aggressive tumors, such as medulloblastoma, ependymoma, and chordoma, efficacy declined over time, though statistical modeling provided valuable insights into these trends.

Toxicity outcomes highlighted low rates of vasculopathy, hearing loss, vision impairment, neurocognitive decline, and endocrine dysfunction, supporting the safety of PT compared to conventional approaches. Nonetheless, risks such as brainstem injury and vascular complications underscore the need for careful planning and long-term follow-up.

Limitations of the literature include heterogeneous reporting of outcomes, surgical margins, molecular stratification, and scarcity of extended follow-up data, which together constrain the ability to make definitive clinical recommendations.

In summary, current evidence supports PT as an important treatment modality in pediatric neuro-oncology, particularly where reduction of late toxicity is a priority. However, the predominance of retrospective data and limited availability of very long-term follow-up necessitate continued prospective study.

Ethics

This study involved analysis of data from previously published literature and did not involve human participants or identifiable patient data. Ethical approval was therefore not required.

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Declaration of Conflicts of Interest

The authors have no conflicts to disclose.

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Data sharing availability

All data analyzed in this study are derived from published literature. No new data were generated or analyzed that are not included in the article or its supplementary materials.

Author contribution

Conception and design of study: JG, PR, JK, MM, RW, JD. Library searches: JG. Writing the manuscript: JG, JK, PR, MAE, MM, RW, JD, AP. Statistical analysis: JG, AP. Critical review and supervision: PR, JK, MAE. All authors reviewed the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijpt.2026.101317.

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