Advances in Radiation Oncology (2023) 8, 101189

advances in radiation oncology

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Critical Review

Proton Radiotherapy for Management of Medulloblastoma: A Systematic Review of Clinical Outcomes

Sympascho Young, MD,[a] Kiran Phaterpekar, BSc,[b] Derek S. Tsang, MD,[c] Gabriel Boldt, MLIS,[a] and Glenn S. Bauman, MD[a,*]

[a]Department of Radiation Oncology, University of Western Ontario, London Regional Cancer Program, London, Ontario, Canada; [b]University of British Columbia, Vancouver, British Columbia, Canada; and [c]Department of Radiation Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

Received 1 December 2022; accepted 27 January 2023

Abstract

Purpose: The aim of this study was to comprehensively review all studies examining clinical outcomes of craniospinal irradiation with proton radiotherapy for medulloblastoma (MB) to determine whether theoretical dosimetric advantages have translated into superior clinical outcomes (including survival and toxicities) compared with traditional photon-based techniques.

Methods and Materials: We performed a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Articles reporting on clinical outcomes of pediatric and/or adult patients with MB treated with proton radiotherapy were included. Evidence quality was assessed using a modified Newcastle Ottawa scale and GRADE score.

Results: Thirty-five studies were included, with a total of 2059 patients reported (representing an estimated 630-654 unique patients). None of the studies were randomized, 12 were comparative, 9 were prospective, 3 were mixed, and 22 were retrospective. Average mean/median follow-up was 5.0 years (range, 4 weeks to 12.6 years). The majority of studies (n = 19) reported on treatment with passive scatter proton beams exclusively. Average study quality was 6.0 out of 9 (median, 6; standard deviation, 1.6). Nine studies scored ≥8 out of 9 on the modified Newcastle Ottawa Scale; an overall "moderate" GRADE score was assigned. Well-designed comparative cohort studies with adequate follow-up demonstrate superior neurocognitive outcomes, lower incidence of hypothyroidism (23% vs 69%), sex hormone deficiency (3% vs 19%), greater heights, and reduced acute toxicities in patients treated with protons compared to photons. Overall survival (up to 10 years), progression-free survival (up to 10 years), brain stem injury, and other endocrine outcomes were similar to those reported for photon radiation. There was insufficient evidence to make conclusions on endpoints of quality of life, ototoxicity, secondary malignancy, alopecia, scoliosis, cavernomas, and cerebral vasculopathy.

Conclusions: Moderate-grade evidence supports proton radiotherapy as a preferred treatment for craniospinal irradiation of MB based on equivalent disease control and comparable-to-improved toxicity versus photon beam radiation therapy.

Sources of support: This work had no specific funding.

Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

All data generated or analysed during this study are included in this published article (and its supplementary materials files).

*Corresponding author: Glenn S. Bauman, MD; E-mail: glenn.bauman@lhsc.on.ca

Introduction

Medulloblastoma (MB) is an embryonal central nervous system (CNS) tumor located in the posterior cranial fossa. It is the most common malignant brain tumor in children, comprising nearly 20% of all pediatric brain

https://doi.org/10.1016/j.adro.2023.101189

tumors. The annual incidence in the United States is approximately 350 to 450 patients per year.[1] Though adults can have MB as well, pediatric incidence is 10 times higher, with peak incidence occurring in children aged 4 to 9 years.

MB comprises a biologically heterogenous group of tumors with a propensity for spread throughout the cerebrospinal space, typically fatal if left untreated. Modern therapy consists of surgical resection to remove the tumor followed by cytotoxic chemotherapy and craniospinal irradiation (CSI) in noninfants (>3 years of age). Treatment outcomes are associated with patient age as well as clinicopathologic and molecular factors. Five-year overall survival (OS) rates for standard-risk MB (defined as patients >3 years of age with gross total resection and no evidence of metastases) is 70% to 85%.[2–5] On the other hand, patients with a subtotal resection, metastasis at diagnosis, or those that are <3 years of age are considered to be high risk and have 5-year OS rates of <70%.[2–5] Contemporary studies have also defined prognostic molecular factors[5] that will guide treatment in the future. However, most of the existing body of literature continues to refer to standard and high-risk stratification.

CSI with a radiation therapy (RT) boost to the tumor bed is an essential component of standard-of-care treatment for children of sufficient age after resection of tumor. However, CSI can be associated with significant long-term toxicities, which include ototoxicity, cataracts or other visual deficits, alopecia, neurocognitive impairment, gonadal dysfunction and fertility issues, bone marrow suppression, cardiopulmonary impairment, endocrine dysfunction, skeletal and soft tissue growth impairment and/or deformities, and radiation-induced secondary malignancies.

Proton radiotherapy (PT) offers the ability to deliver highly conformal dose to target volumes while sparing organs in the neck, thorax, abdomen, and pelvis during the craniospinal phase and surrounding healthy brain during the boost phase of treatment. As such, many institutions in the United States and around the world now use protons to treat patients with MB with the aim of reducing late toxicities in patients. Significant capital and operating costs associated with PT limit its availability worldwide,[6,7] and access to the therapeutic benefits of PT in pediatric populations is a key driver of investment in PT.[8]

Thus far, studies demonstrating superiority of PT have mostly been dosimetric comparisons. Clinical outcome data has been limited. A systematic review of PT for all pediatric CNS tumors published in 2016 found only 3 case series on clinical outcomes of patients with MB.[9] They concluded that there was not enough clinical evidence to support or refute superiority of PT at the time.[9] In the past 6 years, additional clinical data have begun to emerge, and we sought to systematically re-examine this question: Does PT for adjuvant CSI of patients with MB result in improved clinical outcomes and toxicity profiles?

The aim of this study was to provide a comprehensive systematic review of all studies examining clinical outcomes of PT for CSI as adjuvant therapy after resection of MBs in both adults and children. This paper should benefit radiation oncologists, pediatric neuro-oncologists, physicists, and health care system funding bodies by compiling the data into a single source and assessing the quality of the existing body of evidence that examines the benefit of PT for MB.

Methods and Materials

Literature search

We performed a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1). The study was registered with PROSPERO (CRD42022302455). This study was exempt from research ethics board review. Figure 1 is a PRISMA diagram detailing the search, screening, and exclusion of studies based on our predefined inclusion and exclusion criteria.

Search strategy

A systematic search for scientific literature on PT for patients with MB was carried out in the PubMed (MEDLINE), Embase, and Cochrane Central Register of Controlled Trials databases. Due to expected scarcity of reports, no filters were used with respect to language, study design, or date of publication. Search date was December 30, 2021, and all articles from inception to December 30, 2021, were included. Our literature search strategy was developed using medical subject headings (MeSH) and text words with the assistance of a medical librarian (G.B.). To ensure literature saturation, the reference lists of included studies and relevant reviews were also manually searched for any missed relevant source. The first 10 pages of Google Scholar were searched for additional possible relevant articles. The search strategies are shown in Supplementary E1.

Eligibility criteria

We included case series of ≥5 patients, prospective and retrospective comparative cohort studies, case-control or nested case-control studies, cross-sectional studies, single-arm clinical trials, randomized controlled trials, and systematic reviews. We excluded dosimetric comparisons, simulation studies, case reports, case series of <5 patients, toxicity risk modeling studies, animal studies, descriptive or narrative studies, feasibility assessments, cost-

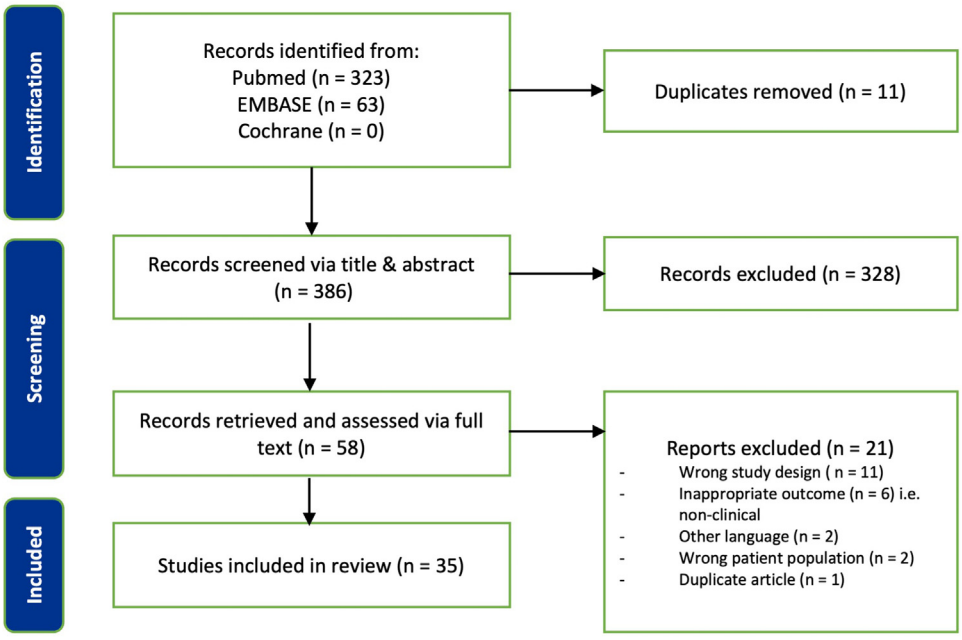


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

effectiveness analyses, letters, news reports, editorials, reviews, notes, or conference abstracts.

Two authors (S.Y., K.P.) independently reviewed all titles and abstracts for eligibility using Covidence software (Melbourne, Australia); discrepancies were resolved either by consensus or approaching a third researcher (G.S.B.) for adjudication. Two researchers also independently conducted full-text review using the following PICO (Population, Intervention, Comparator, Outcomes) eligibility criteria (Table 1).

Population

Patients must have pathologic diagnoses of MB. Supratentorial primitive neuroectodermal tumor histologies were excluded. All patients were included regardless of age, including both pediatric and adult patients, due to the scarcity of studies anticipated. Studies that report on multiple diagnoses were only included if there were ≥5 patients with MB and information of follow-up and outcomes were available for this subgroup of patients (either reported as a MB group or reported for individual patients).

Table 1 PICO selection criteria

PICO selection criteria	Inclusion criteria	Exclusion criteria
Population	Both adults and children with medulloblastoma	
Intervention	Proton radiotherapy for CSI	Photon radiotherapy only, carbon ion therapy, studies in which CSI or tumor boost were not described (ie, non−standard of care)
Comparator	Photon therapy for CSI (studies with no comparator arm allowed as well)	
Outcomes	Clinical effectiveness/survival outcomes, secondary malignancies, acute side effects, long-term toxicities, health-related quality of life	Cost effectiveness, dosimetric outcomes, risk modeling
Study designs	Case series of >5 patients with medulloblastoma, prospective and retrospective comparative cohort studies, case-control or nested case-control studies, cross-sectional studies, and clinical trials	Case reports, case series ≤5 patients, animal studies, descriptive/narrative studies, feasibility assessments, letters, news reports, editorials, reviews, and congress abstracts
Language	English	Languages other than English

Abbreviation: CSI = craniospinal irradiation; PICO = Population, Intervention, Comparator, Outcomes

Intervention

We included studies using PT as adjuvant treatment for MB after surgical resection. Eligible patients must have received resection followed by CSI followed by a tumor boost, which is the contemporary standard-of-care technique for patients of sufficient age. Studies which did not describe CSI or tumor boost were excluded. We excluded studies solely examining photon radiation or other forms of radiation (such as carbon ions) for MB.

Comparator

Comparative studies comparing proton and photon-treated cohorts were included. We also included studies that report only on proton-treated cohorts, due to the low anticipated number of comparative studies. However, we did not include studies that only reported photon-treated cohorts, as many photon-only cohorts are from historical studies with older RT treatment techniques, no chemotherapy (or premodern regimens), older surgical techniques, and different patient risk classifications. As such, it would have been difficult to draw meaningful toxicity comparisons with PT from the modern era. Instead, we use toxicity and disease control outcomes from 3 modern-era benchmark photon trials for comparison: the COG A9961 phase 3 study,[2] the St. Jude Medulloblastoma-96 study,[3] and the more recent ACNS0331 trial.[4]

Outcomes

We only included studies that report clinical endpoints. We included all clinical endpoints reported (Table 2), whether assessed objectively, by physician-assessed criteria, or by patient-reported questionnaires.

Other

There were no restrictions regarding length of follow-up of outcomes. There were no restrictions by type of setting.

Language

While our initial search criteria did not exclude articles by language, our full-text analysis only included articles reported in English. There were 2 possibly relevant titles in other languages, which are provided in Supplementary E2.

Data extraction

Data were extracted in duplicate by 2 independent investigators (S.Y., K.P.) and data were uploaded to Microsoft Excel (Microsoft Corp, Redmond, WA). Discrepancies were resolved by consensus. Where reported information was unclear, study authors were contacted by email for additional information and clarification of study data.

Quality appraisal

Individual study quality was scored using a modified Newcastle Ottawa Scale (NOS) for cohort studies (Supplementary E3).[10] To ensure reliability of scores, 2 independent assessors (S.Y., K.P.) assigned scores, and discrepancies were resolved by consensus. A maximum of 4 points were given based on selection of the proton and photon cohorts, a maximum of 2 points for comparability of the cohorts, and a maximum of 3 points for outcome (assessment of outcome, duration of follow-up, and number of patients lost to follow-up). The highest quality studies received a maximum score of 9. The quality of the overall evidence base was assessed by National Academy of Medicine GRADE scale.[11]

Results

We identified 386 unique articles. Of these, 35 primary studies qualified for inclusion (Fig. 1), with a total 2059 patients reported (representing an estimated 630-654 unique patients) (Table 3). Number of unique patients was calculated by using reported numbers from the paper with the largest cohort/longest follow-up from each institution and cross-checking the enrollment years/cohort characteristics with other publications to identify any patients who were not included in the first publication (Supplementary E5). Publication dates ranged from 2011 to 2021. The majority of studies (n = 32) were from the United States, with 17 studies from researchers affiliated with Massachusetts General Hospital (MGH). Other countries of origin included Japan (n = 1), South Korea (n = 1), and Switzerland (n = 1). None of the studies were randomized, 12 were comparative, 9 were prospective, 3 were mixed, and 22 were retrospective. Average mean/median follow-up was 5.0 years (range, 4 weeks to 12.6 years). The majority of studies (n = 19) reported on treatment with passive scatter proton beams exclusively. Average study quality was 6.0 out of 9 (median, 6; standard deviation [SD], 1.6). Nine studies scored ≥8 out of 9 on the NOS (Table 3, Supplementary E4). An overall "moderate" GRADE score was assigned.

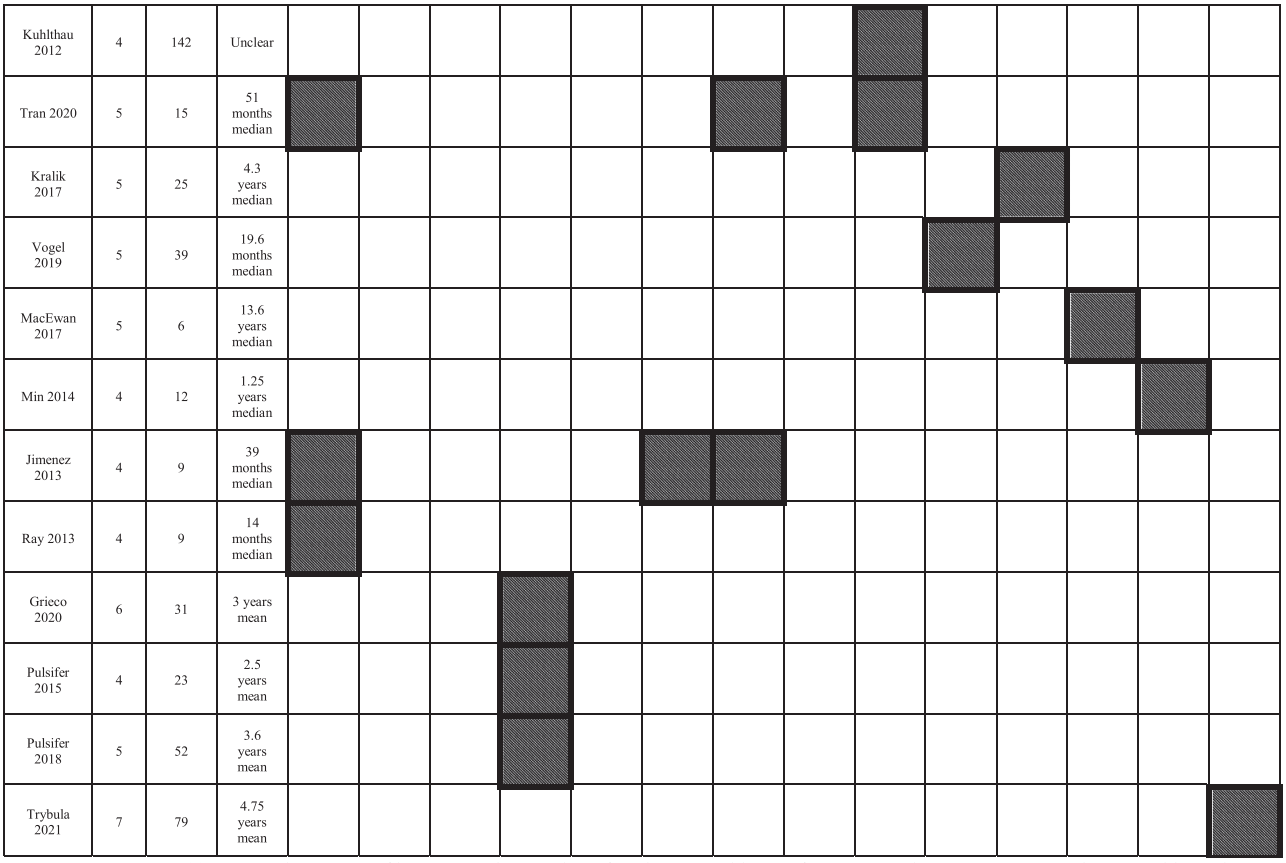
An overview of included studies, endpoints reported, and quality of endpoints is provided in Table 2 (with details in Table 3) and findings are summarized narratively in the following.

Disease control and secondary malignancy

Thirteen studies reported on disease control outcomes, the primary endpoint for 9 studies; however only 3 of the 9 studies had sufficient durations of follow-up (defined as follow-up >5 years). One of these was a cohort of 178 patients treated with PT from MGH with a median

Table 2 Overview of study endpoints reported

Study	NOS score (/9)	Sample size included in analysis	Reported median or mean FU (PT cohort)	Disease Control	Patterns of Failure	Secondary malignancy	IQ	Hypothyroidism	Other endocrinopathies	Ototoxicity	Acute toxicity	HrQOL	Brainstem Injury	RLVCVL	Scoliosis/ Height	Alopecia	Cavernoma
Paulino 2021	8	115	8.7 years median	↔													
Eaton 2016	9	88	6.2 years median	↔	↔												
Baliga 2021	6	178	9.3 years median	↔									↔				
Sethi 2014	5	109	38.8 months median		↔												
Eaton 2021	8	37	5.3 years median				↓										
Kahalley 2020	9	79	3.7 years mean				↓										
Eaton 2016	9	77	5.8 years median					↓	↔						↓		
Aldrich 2021	6	118	5.6 years median					↓	↔								
Bielamowicz 2018	7	95	3.8 years median					↔									
Paulino 2018	8	84	56 months median							↔							
Yock 2016	6	59	5.2 years median	↔													
Brown 2013	8	40	2.2 years median								↓						
K Liu 2021	8	97	8.1 years median	↔							↓						
Song 2014	8	43	22 months median								↓						
Gentile 2018	6	151	4.2 years median										↔				
Giantsoudi 2016	6	111	4.2 years median										↔				
Vatner 2018	5	130	4.4 years median														
Moeller 2011	5	19	11 months mean														
Hashimoto 2019	5	178	4 weeks														
I Liu 2021	4	20	3.1 years median														
Suneja 2013	3	48	None														
Eaton 2020	5	40	6.7 years median														
Kamran 2018	6	116	5 years median														



Primary □ outcome(s) Reported outcome of low or very low quality of evidence, unable to inform ■ conclusion outcomes with reasonable evidence; ↔ PT effect comparable to photons ↓ PT has reduced toxicity compated to photons.

follow-up of 9.3 years. The other 2 studies were matched cohort studies with >5 years of follow-up in both proton and photon cohorts, and both scored ≥8 out of 9 on the NOS. OS (≤10 years), progression-free survival (≤10 years), and patterns of failure were comparable between these series. Ten-year OS ranged from 85.3% to 86.9% for standard-risk patients with MB treated with PT. The 10-year cumulative incidence of secondary malignancy was also lower for proton cohorts (2.1%-4.9% vs 8%) in the 2 studies comparing photons and protons but did not reach statistical significance in any individual study.

Neurocognitive outcome

Two matched cohort studies demonstrated superior cognitive outcomes in patients treated with PT compared with photons; both studies scored ≥8 out of 9 on the NOS and had follow-up durations ranging from 3.7 to 5.3 years. Patients treated with PT showed stable global IQ and working memory over time whereas patients treated with photons lost a statistically significant 0.9 global IQ points per year ($P = .009$) and 2.2 points in working memory per year ($P = .001$) on average.[19] In addition, patients also had better perceptual reasoning outcomes and verbal comprehension after PT versus photon-treated patients. Processing speed declined similarly in PT and photon-treated patients in both studies.

Endocrinopathy

Four studies reported on endocrine results; 1 scored ≥8 out of 9 on the NOS. In series including a comparison with photon cohorts and with follow-up >5 years, PT was associated with significantly lower incidence of hypothyroidism (23% vs 69%; $P = .001$). This was consistent for both central and peripheral hypothyroidism. In addition, PT was associated with lower incidence of sex hormone deficiency (3% vs 19%; $P = .025$) and greater heights (mean ± SD, −1.19 ± 1.22 vs −2 ± 1.35; $P = .02$) at follow-up. The incidence of other endocrinopathies,

Table 3 Overview of included studies on proton radiotherapy for patients with MB

Study* and NOS score (score/9)†	Method	Patient characteristics	FU	Treatment details	Control group	Select reported outcomes	Statistical methods for incidence rate	Comments
Disease control (n = 5)								
Paulino et al (2021); Houston (United States)[12] 8/9★	Retrospective; comparative by time-frame; enrollment from 1996-2014	- 115 patients, including 52 patients treated with PT and 63 patients treated with photon therapy - Median age was 7.0 y in both groups (range, 3-17 y) - 73/115 patients had standard-risk MB	Median FU (PT): 8.7 y (0.4-13.4 y); median FU (photon): 12.8 y (0.2-20.3 y)	No details on surgery; variable chemotherapy protocols; passive scatter 3DCPT	52 patients who had photon RT from 1996-2006 compared with PT cohort from 2007-2014 at the same institution	- OS (5 y) was similar for the PT and photon cohorts (80.3% and 80%, respectively) - OS (10 y) was similar for PT and photon cohorts (72.4% and 78.1%, respectively) - For standard-risk patients, 5- and 10-y OS were 84.5% and 84.5%, respectively, for photon cohort and 93.8% and 85.3%, respectively, for the PT cohort ($P = .55$) - For high-risk patients, the 5- and 10-y OS were 68.5% and 63.2%, respectively, for photon cohort and 56.1% and 49.9%, respectively, for PT cohort ($P = .40$) - 10-y secondary malignancy incidence was 8% for the photon and 4.9% for the PT cohort ($P = .74$) - There was no difference in the distribution of patients according to sex, age at RT (≤7 or >7 y), risk category, CSI dose (18.0-23.4 vs 30.6-39.6 Gy), or type of chemotherapy - Median patient age at time of RT was 7.1 y for group I and 7.0 y for group II	Actuarial rate using Kaplan-Meier method	Robust study. Photon and proton cohort drawn from different time frames at the same institution. FU shorter for PT (8.7 y) vs photon (12.8 y) cohort. Otherwise, no significant differences between cohorts for sex, age, risk category, CSI dose, or chemotherapy regimen. Molecular subtyping data not reported (likely not available at that time).
Eaton et al (2016);[13] Boston and Atlanta (United States) 9/9★	Retrospective; comparative from 2 institutions; enrollment from 2000-2009	- 88 standard-risk patients, including 45 patients treated with PT and 43 patients treated with photon therapy - Median age was 6.2 y (range, 3-21 y) in the PT cohort and 8.3 y (range, 3.4-19.5 y) in the photon cohort	Median FU 6.2 y for PT (95% CI, 5.1-6.6 y) and 7.0 y for photon therapy (95% CI, 5.8-8.9 y)	Maximal safe resection; all received chemotherapy (variable protocols); passive scatter 3DCPT	43 patients who had photon RT (different institution within the same timeframe)	- OS (6 y) similar for the PT and photon patients was 82.0% (95% CI, 65.4%-91.1%) and 87.6% (95% CI, 72.7%-94.7%), respectively - Matched 1:1 sample of 25 PT and photon patients confirmed no significant difference in OS - RFS (6 y) similar for PT and photon patients was 78.8% (95% CI, 63.0-89.0) and 76.5% (95% CI, 60.6-86.6), respectively - Patterns of failure similar between 2 cohorts - Secondary malignancy in PT and photon patients was 0 and 3, respectively	Actuarial survival rate using KP curves	Robust study. Photon and proton comparative cohorts drawn from different institutions (Emory/MGH) in same timeframe; cohort characteristics were reasonably similar, although median age was 2 y older in photon group. Median FU similar between cohorts: 6.2 y (PT) vs 7.0 y (photon). Molecular subtyping data not reported (likely not available at that time).
Baliga et al (2021)[14]; Boston (United States) 6/9★	Mixed (mostly prospective); enrollment from 2002-2016	- 178 patients - 102 (57%) standard-risk, 16 (9%) intermediate-risk, 60 (34%) high-risk patients - Median age was 8.1 y (2.5-24.1 y)	Median FU 9.3 y (0.5-17.2 y)	Variable extent of surgery, 159 (89%) underwent GTR, variable chemotherapy protocols; passive scatter + pencil beam scanning PT	No	- OS (10 y) was 79.3% (95% CI, 73.1%-85.9%) for the entire cohort - OS (10 y) standard risk was 86.9% (95% CI, 79.9%-94.4%) - OS (10 y) IR/HR was 68.9% (95% CI, 58.7%-80.8%) - 10-y cumulative incidence of brain stem injury was 1.9% (95% CI, 0.5%-5.1%) - 10 y cumulative incidence of secondary malignancy was 2.1% (95% CI, 0.6%-5.8%) - Median time to progression was 1.6 y (0.22-10.3) - EFS (10 y) standard risk was 79.5%	Actuarial rate: Cox and Fine-Gray model for competing risks	Longest FU reported on the MGH proton cohort (median, 9.3 y). No comparative photon group. Molecular subtyping data not reported (likely not available at that time).

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Jimenez et al (2013)[15]; Boston (United States) 4/9 Individual patient data reanalyzed	Retrospective; cohort; enrollment from 2002-2010	- Cohort of 15 very young patients with MB/SPNET, including 12 patients with MB - 9 patients with MB underwent CSI (included in our analysis) - Median age was 37 mo (23-55 mo)	Median FU 39 mo (3-102 mo)	Maximal safe resection; all received chemotherapy (variable protocols); passive scatter 3DCPT	No	- Hearing loss in 7/9 patients (77.8%) - Grade 2 endocrinopathy in 2/9 patients (22.2%) - LF (3 y): 0/9 patients (0%) - OS (3 y): 9/9 patients (100%)	Actuarial rate by Kaplan-Meier	Small cohort of very young patients with SPNET/MB with only 9/15 patients fitting our study criteria (CSI excluded or delayed in some patients due to young age). Individual patient data available for reanalysis. FU duration insufficient for OS or endocrinopathy.
Ray et al (2013)[16]; Indianapolis (United States) 4/9 Individual patient data reanalyzed	Retrospective; cohort; enrollment from 2004-2012	- 22 pediatric patients with leptomeningeal spinal metastases - 9 patients with MB - Mean age was 5.7 y (range, 2-11 y)	Median FU 14 mo (4-33 mo)	No details	No	- Local control (12 mo) was 68% for entire cohort - OS: 7/9 for patients with MB (77.8%)	Crude rate, patients were simply censored at last known date alive	Small cohort of patients with multiple diagnoses with leptomeningeal spine metastasis. Individual patient available; 9 patients with MB fit study criteria. Data were reanalyzed but FU was insufficient to draw conclusions about OS or local control.
Patterns of failure (n = 1)								
Sethi et al (2014);[17] Boston (United States) 5/9	Retrospective; cohort; enrollment from 2002-2011	- 109 patients with MB - Median age was 7.4 y (range, 2.2-22.7 y) - 74 (68%) standard-risk and 35 (32%) high-risk patients	Median FU 38.8 mo (range, 1.4-119.2 mo)	Variable (including surgery and chemotherapy); passive scatter 3DCPT	No	- Patterns of failure similar to historical photon cohorts: supratentorial (n = 8), spinal (n = 11), posterior fossa (n = 5) - LET distribution calculated by Monte Carlo, no correlation between recurrence and low LET - Local failure was 16/109 (15%) - OS was 97/109 (89%) - Median time to recurrence was 18.6 mo (range, 2.8-38.9 mo)	Patterns of failure reported; descriptive crude statistics	Study reported sites of local relapse in photon and proton cohort. No difference in patterns of failure or correlation between recurrence and LET distribution. FU duration insufficient for OS or disease control outcomes.
Neurocognitive Outcome (n = 5)								
Eaton et al (2021)[18]; Boston (United States) 8/9★	Prospective; cohort; comparative from 2 institutions; enrollment from 2000-2009	- 37 patients with MB with neurocognitive data (17 patients treated with PT; 20 patients treated with photon radiation) - Median age of PT cohort was 7.3 y (range, 3.4-20 y) - Median age of photon cohort was 8.1 y (range, 4.5-16.6 y) - All standard-risk patients with MB	Median FU in PT cohort: 5.3 y (range, 1-11.4 y) Median FU in photon cohort: 4.6 y (range, 1.1-11.2 y)	All patients underwent maximal safe resection of the primary tumor and chemotherapy; patients received 3DCPT in PT cohort and 3DCRT or IMRT in photon cohort	50 patients' propensity score matched 1:1 PT cohort of 25 obtained from MGH; photon cohort of 25 obtained from Emory University; same timeframe	- Patients treated with PT performed higher in IQ scores (P = .021), verbal comprehension (P = .01), and perceptual reasoning (P = .011) at FU compared with patients treated with photon radiation - PT cohort was comparable to the photon cohort in relation to processing speed (P = .331) and working memory (P = .388) - Photon cohort had higher degree of variation in outcomes, that is, more severe declines	Use of descriptive statistics with different IQ/cognitive scales. N/A no actuarial methods	Multi-institutional case-matched cohort study with 5.3-y median FU for proton-treated patients (longest FU). Proton cohort was drawn from MGH; photon cohort was drawn from Emory University. Household incomes were significantly different from each other, but researchers found no association between household income and FSIQ. Other baseline characteristics (age, FU time) were similar. Baseline neurocognitive measurements were only taken for the proton cohort, not the photon cohort.
Kahalley et al (2020)[19]; Toronto (Canada) and Houston (United States) 9/9★	Retrospective; comparative; enrollment from 2007-2018	- 79 patients with MB - 37 patients treated with PT; 42 patients treated with photon therapy - Mean age at diagnosis was 8.9 y (3.5-14.4 y) for patients treated with PT - Mean age at diagnosis was 8.4 y (3.6-15.3 y) for patients treated with photon therapy - 57/79 patients had standard-risk MB	Mean FU within the PT cohort: 3.7 y (range, 0.1-10.9 y) Mean FU within the photon cohort: 4.8 y (range, 0.9-9 y)	All patients underwent craniotomy; SJMB03 or SJMB12 chemotherapy protocols; Unspecified RT technique	42 patients treated with photon RT from 2007-2018 in Canada were compared with a matched PT cohort using the same protocols and within the same timeframe	- Patients treated with PT exhibited stable intellectual outcomes in most domains and had significantly better long-term global IQ (P = .009), perceptual reasoning (P = .022), and working memory scores (P = .002) after 4 y compared with patients treated with photons - Change in verbal comprehension score were not statistically different between PT and photon cohorts - Processing speed declined similarly in both cohorts (P = .003)	Use of descriptive statistics with different IQ/cognitive scales. N/A no actuarial methods	Multi-institutional matched cohort study with median FU 3.7 y for proton cohort. Proton cohort drawn from Texas Children's Hospital; photon cohort drawn from the Hospital for Sick Children (Canada) in same timeframe. Clinical and demographic variables were not significantly different from each other. Cohorts were matched by risk type, age, sex, maternal education, and paternal education. Baseline scores were missing for 15 photon and 4 PT patients.

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Pulsifer et al (2015)[20]; Boston (United States) 4/9	Retrospective; enrollment from 2002-2013	– 23 patients with MB out of the total sample (N = 60) – Mean age of all patients: 12.3 y (range, 6.3-21.7 y)	Mean FU: 2.5 y for all patients (range, 1-8.3 y)	12 patients received a biopsy; 20 patients received near/STR; 26 patients received GTR; 37 patients received chemotherapy; patients treated with passive scatter 3DCPT	None	– No significant change in IQ, verbal comprehension, perceptual reasoning, or working memory at FU – Processing speed declined significantly (P = .003) in patients who received CSI, with a greater decline in younger patients (<12 y) at diagnosis and those with the highest baseline scores	Use of descriptive statistics with different IQ/cognitive scales. N/A no actuarial methods	Early report of pediatric CNS patients treated with PT from MGH; mixed diagnoses, only 23/60 were patients with MB treated with CSI. Demographic and treatment information available for patients treated with CSI. Small sample size, short median FU of 2.5 y.
Pulsifer et al (2018)[21]; Boston (United States) 5/9	Prospective; cohort; enrollment from 2002-2017	– 52 patients with MB out of total sample (N = 155) – Mean age of all patients: 8.9 y (range, 1-22.5 y)	Mean FU: 3.6 y (range, 1.1-11.4 y) for all patients	18 patients received biopsy, 54 patients received near/STR, 79 patients received GTR; 98 patients received chemotherapy; patients received passive scatter 3DCPT	None	– Overall, mean IQ declined slightly at FU for the entire cohort – Significant IQ decline in patients <6 y old who were receiving CSI – Adaptive functioning score declined in patients who received CSI and were <6 y of age, but improved in older patients (>6 y) – IQ values were in the average range at baseline/FU for the total sample	Use of descriptive statistics with different IQ/cognitive scales. N/A no actuarial methods	Update from author in previous row with median FU of 3.6 y. Also a cohort with mixed diagnoses; 55/155 were patients with MB treated with CSI. IQ and demographic data were not available separately for MB subgroup; therefore, conclusions cannot be drawn regarding our research question. Only 73% of patients followed up with for cognitive functioning and IQ, but 147/155 patients followed up with for adaptive functioning.
Grieco et al (2020)[22]; Boston (United States) 6/9	Retrospective; nested case control; no enrollment dates provided	– 58 patients with posterior fossa tumor included in the study – 31 patients with MB eligible for the study – Mean age 7 y (range, 1.2-15.8 y)	Mean FU: 3 y (SD, 2.24)	Median of 35day interval between surgery and PT; 29 patients underwent GTR, 7 patients underwent STR; 31 patients had chemotherapy; all treated with passive scatter 3DCPT	All patients received PT; 18 patients who had CMS (16/18 MB) were matched with 18 non-CMS patients (15/18 MB)	– 18 patients (31%) developed postoperative pediatric CMS – Longitudinal neuropsychological outcomes for postoperative pediatric patients with CMS who underwent PT did not differ significantly from those without CMS who underwent PT – At 3 y, overall intelligence, receptive/expressive vocabulary, behavioral inhibition, emotional control, mood, anxiety were in normal ranges. – Fine motor skills were impaired in all patients	Use of descriptive statistics with different IQ/cognitive scales. N/A no actuarial methods	Longitudinal study looking at neuropsychological outcomes of PT-treated patients with postoperative pediatric CMS vs matched controls. Note that comparator cohort is not a photon cohort, rather were also patients treated with protons.
Endocrinopathy (n = 4)								
Eaton et al (2016)[23]; Boston (United States)9/9★	Retrospective; comparative; enrollment from 2000-2009	– 77 patients with MB, including 40 patients treated with PT and 37 patients treated with photon therapy – Median age for patients treated with PT: 6.2 y (range, 3.3-21.9 y) – Median age for patients treated with photon therapy: 8.3 y (range, 3.4-19.5 y) – All patients had standard-risk MB	Median FU for patients treated with PT: 5.8 y (range, 3.4-9.9 y) Median FU for patients treated with photon therapy: 7 y (3.5-13.5 y)	Maximal safe resection; chemotherapy protocol of vincristine, cisplatin, cyclophosphamide, and/or lomustine; passive scatter 3DCPT	37 patients with MB treated by photon CSI. Patients in the proton cohort came from MGH, while patients in the photon cohort came from Emory University; same timeframe for both cohorts	– PT was associated with reduced risk of hypothyroidism compared with photon cohort (23% vs 69%, P = .001), sex hormone deficiency (3% vs 19%; P = .025), and requirement for endocrine replacement therapy (55% vs 78%; P = .03) – Greater height SD score in the PT cohort vs photon cohort (mean ± SD: −1.19 ± 1.22 vs −2 ± 1.35; P = .02) – No significant difference in incidence of growth hormone deficiency (53% vs 57%, P = .708), adrenal insufficiency (5% vs 8%, P = .667), or precocious puberty (18% vs 16%, P = .881)	Crude rate; only survivors analyzed; therefore, no competing risk required	PT cohort was significantly younger than photon cohort, but cohorts were similar in other respects (ie, sex, risk type). Median FU was slightly longer for photon vs PT cohort (7 vs 5.8 y), but FU duration was sufficient for endpoint of interest in both cohorts. Photon cohort was drawn from Emory University; proton cohort was drawn from MGH. Endocrine outcomes were assessed after the diagnosis was made (referenced medical records).

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Aldrich et al (2021)[24]; Houston (United States) 6/9★	Retrospective; comparative; enrollment from 1997-2016	- 118 patients with MB, including 64 patients treated with PT and 54 patients treated with photon therapy - Mean age of patients treated with PT: 6.83 y (SD, 3.2) - Mean age of patients treated with photon therapy: 8.47 y (SD, 4.04) - Age range of total sample (2-18 y) - 77 patients had average-risk MB and 41 patients had high-risk MB	Median FU for all patients: 5.6 y (range, 1-10 y)	Maximal resection in all patients; multiagent chemotherapy; passive scatter PT	54 patients treated with photon CSI at Texas Children's Hospital (same institution); separate propensity score 1:1 match (although never stated explicitly, these appear to be the same patients as used in Bielamowicz et al[25] study)	- The PT cohort had a significantly lower incidence of primary hypothyroidism compared with photon cohort (6% vs 28%; HR, 4.61; 95% CI, 1.2-17.66; $P = .03$) - Central hypothyroidism was found to be statistically similar between the cohorts (HR, 2.35; 95% CI, 0.81-6.82) - Rates of adrenal insufficiency (HR, 1.07; 95% CI, 0.41-2.81) and GH deficiency (HR, 0.71; 95% CI, 0.43-1.17) were comparable between PT and photon cohorts - On a 1:1 propensity score-matched comparison, central hypothyroidism was significantly lower in PT patients ($P = .01$)	Actuarial rate estimated with KP	Not explicitly stated, but patient population likely overlaps significantly with Bielamowicz et al.[25] Median FU was 5.6 y for all patients (but was not reported separately for proton/photon patients). Likely suffers from same weakness as Bielamowicz study, where FU for PT cohort was shorter than photon cohort; however, in this study, "thyroid studies were not routinely obtained prior to initiation of radiotherapy." Cannot determine whether hypothyroidism was present before RT
Bielamowicz et al (2018)[25]; Houston (United States) 7/9★	Retrospective; comparative; enrollment from 1997-2014	- 95 patients with MB, including 41 patients within a PT cohort, and 54 patients within a photon therapy cohort - Median age for patients treated with PT: 7 y (range, 2.3-14.4 y) - Median age for patients treated with photon therapy: 8.2 y (range, 2-18 y) - 25 standard-risk patients with MB and 15 high-risk patients with MB within the PT cohort - 41 standard-risk and 13 high-risk patients with MB within the photon cohort	Median FU for patients treated with PT: 3.8 y (range, 1-8.8 y) Median FU for patients treated with photon therapy: 9.6 y (range, 1-15.8 y)	Maximal resection in all patients; all patients treated with chemotherapy, variable protocols; passive scatter PT	54 patients treated with photon CSI. All patient medical records came from Texas Children's Hospital (1997-2007)	- Incidence of hypothyroidism in the PT cohort was numerically lower than the photon cohort but did not reach statistical significance (19% vs 46.3%; HR, 1.85; $P = .14$) - Primary hypothyroidism was numerically but not significantly lower in PT cohort compared with photon cohort (15.8% vs 22.2%; HR, 2.1; $P = .27$) - Central hypothyroidism was numerically but not significantly lower in PT cohort compared with photon cohort (18% vs 24%; HR, 2.16; $P = .18$)	Crude rate 84/95 patients alive at time of analysis	Significantly longer median FU for photon-treated patients compared with PT (9.6 vs 3.8 y). Patients all had preradiation thyroid function labs. Cohorts are similar in age, sex, and risk type. No other characteristics described.
Vatner et al (2018)[26]; Boston (United States) 5/9	Prospective; enrollment in 3 prospective studies from 2003-2016	- 222 patients with brain tumors - 130 eligible MB with CSI - Median age of all patients: 7.4 y (range, 1.1-25.9 y)	Median FU: 4.4 y (range, 0.1-13.3 y)	All patients with MB resected and underwent chemotherapy (variable protocols); passive scatter 3DCPT	No	- 5-y actuarial rates: any hormone deficiency (55.5%), growth hormone (44.2%), thyroid hormone (25.8%), adrenocorticotropic hormone (8%), and gonadotropin (5.1%) deficiencies - 3.7% of patients with MB had endocrinopathies before treatment - Cumulative incidence of primary hypothyroidism was 3% after CSI (significantly lower than other reports) - Median hypothalamic and pituitary RT dose, younger age, and longer FU time associated with increased rates of endocrinopathy	Actuarial rate by KP methods	Single-cohort study. Patients had evaluation of baseline endocrinopathies.
Ototoxicity (n = 3)								
Paulino et al (2018)[27]; Houston (United States) 8/9★	Retrospective; enrollment from 1997-2013	- 84 patients with MB, including 38 patients treated with PT and 46 patients treated with photon therapy - Median age for the PT cohort: 7.6 y (range, 2.9-14.5 y) - Median age for the photon therapy cohort: 9 y (range, 3-18 y) - 24 standard-risk and 14 high-risk patients with MB within the PT cohort - 34 standard-risk and 12 high-risk patients with MB for the photon cohort	Median FU in the PT cohort: 56 mo (range, 17-101 mo); Median FU in the photon therapy cohort: 66 mo (range, 13-163 mo)	Maximal safe resection in all; cisplatin-based chemotherapy delivered 4 wk after RT; amifostine was provided for all PT patients and 19 photon patients (41%); passive scatter PT	46 patients treated with photon IMRT within the same timeframe and at the same institution	- Patients treated with either proton or photon RT had similar grade 3 and 4 ototoxicity rates according to 4 scoring systems despite the proton cohort having a lower mean cochlear dose, lower mean cisplatin dose, and higher rates of amifostine	Actuarial rate by KP methods	Solid comparative study. Median FU of 56-66 mo adequate for ototoxicity outcome. Mean cochlear dose and mean cisplatin dose was reported. Audiograms scheduled before and after RT.

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Yock et al (2016)[28]; Boston (United States) 6/9	Prospective single-arm phase 2 trial; enrollment from 2003-2009	- 59 patients with MB - Median age: 6.6 y (range, 3-21 y) - 39 standard-risk, 6 intermediate-risk, and 14 high-risk patients with MB	Median FU: 5.2 y (IQR, 5.2-8.6 y)	Maximal safe resection; all patients treated with chemotherapy, variable protocols; passive scatter PT	No	- Cumulative incidence of grade 3-4 hearing loss was 12% at 3 y (95% CI, 4%-25%) and 16% at 5 y (95% CI, 6%-29%) according to Pediatric Oncology Group ototoxicity scale - Hearing at 5-y FU was the same/improved compared with baseline in 35% of ears and worsened in 65% of ears - 3-y PFS was 83% (95% CI, 71%-90%); 5-y PFS and OS were 80% (95% CI, 67%-88%) and 83% (95% CI, 70%-90%), respectively - Cumulative incidence of any neuroendocrine deficit at 7-y FU was 63% (95% CI, 48%-75%) - 7-y cumulative incidence of GH and thyroid deficiency was 55% (95% CI, 40%-68%) and 26% (95% CI, 15%-38%), respectively - Perceptual reasoning and working memory did not significantly change at last FU - Verbal comprehension and processing speed declined significantly at last FU ($P < .0001$)	Actuarial estimation of cumulative risk (competing risk considered)	Early longitudinal study reporting on several outcomes of MGH proton cohort including IQ, ototoxicity, endocrinopathies, and survival outcomes. Median FU of 5.2 y adequate for most outcomes.
Moeller et al (2011)[29]; Houston (United States) 5/9	Prospective; enrollment from 2006-2009	- 19 patients with MB - Mean age: 6 y (range, 3-16 y) - 16 standard-risk and 3 high-risk patients	Mean FU: 11 mo (range, 8-16 mo)	All patients received platinum-based chemotherapy; no surgical details; passive scatter PT	No	Hearing sensitivity declined postradiation for all frequencies tested (0-9 kHz, $P < .05$) Preservation of hearing in the audible speech range (0.5-6 kHz) Rate of high-grade ototoxicity (according to Brock Ototoxicity Scale) was 5% Hearing amplification recommended in 3/19 patients posttherapy	Crude rate. No discussion of competing risks	Small sample size, FU duration too short for measurement of outcome. No details on chemotherapy dose received for patients.
Acute toxicity (n = 5)								
Brown et al (2013)[30]; Houston (United States) 8/9★	Retrospective; comparative; enrollment from 2003-2011	- 40 patients with MB treated with VBS CSI - 19 patients with MB treated with PT radiation; 21 patients treated with photon radiation - Median age within the PT cohort was 29.9 y (range, 16.9-49.9 y) - Median age for the photon cohort was 32.7 y (range, 16.6-60.4 y - 14 average-risk patients and 5 high-risk patients in the PT cohort - 14 average-risk and 5 high-risk patients in the photon cohort	Median FU in PT cohort: 2.19 y; median FU in photon cohort: 4.76 y	All patients underwent surgical resection of primary tumor; chemotherapy variable	21 adult patients treated with photon CSI within the same institution	- PT cohort lost less weight than photon cohort (−1.2% vs −5.8%, respectively; $P = .004$) and had fewer patients with >5% weight loss (16% vs 64%, $P = .004$) - PT cohort experienced less grade 2 nausea and vomiting than photon cohort (26% vs 71%; $P = .004$) - PT cohort had less myelosuppression: reduction in peripheral WBC, hemoglobin, and platelets compared with photon cohort ($P \leq .05$) - Similar results seen after excluding patients who received chemotherapy pre-CSI - 2-y OS and PFS both 94% for PT cohort vs 90% and 85%, respectively, for photon cohort - PT cohort less likely to have medical management of esophagitis (5% vs 57%; $P < .001$)	Crude rate	Comparative study of adult patients treated with PT vs photons from MD Anderson. FU of 2.2 y for protons sufficient for assessment of acute toxicities.

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Liu et al (2021)[31]; Boston (United States) 8/9★	Retrospective; comparative; multi-institutional; enrollment from 2000-2017	– 97 patients with MB; 60 patients treated with PT; 37 patients treated with photon therapy – Median age within the PT cohort was 7.5 y (range, 3.5-22.2 y) – Median age within the photon cohort was 9.9 y (range, 3.6-19.5 y) – 52 (87%) standard-risk and 8 (13%) high-risk patients within the PT cohort – 33 (89%) standard-risk and 4 (11%) high-risk patients within the photon cohort	Median FU in PT cohort was 8.1 y (range, 0.2-13.7 y) Median FU in the photon cohort was 7.1 y (range, 0.2-17.5 y)	53 patients from the PT cohort and 35 patients from photon cohort received concurrent chemotherapy; 57 vs 36 patients received post-RT chemotherapy in PT and photon cohort, respectively; no detailed information provided about surgeries; double scatter PT; VBS for patients >15 y	37 patients treated with photon RT in the same timeframe at various institutions; only included patients who received RT alone or with concurrent single agent vincristine to limit confounding effect of chemotherapy agents	– Higher rates of leukopenia (P = .044), lymphopenia (P < .0001), anemia (P = .011), and thrombocytopenia (P = .066) in the photon cohort compared with the PT cohort – No difference in WBC counts, neutrophil counts, or hemoglobin concentration between cohorts – 5-y OS rates not statistically different between the PT and photon cohort (89.6% vs 93.4%; P = .2129) – Similar hematological results seen when comparing non-VBS PT therapy to photon therapy – Monocyte counts were significantly lower in the PT cohort at various times compared with the photon cohort – Platelet counts and lymphocyte counts were significantly higher in the PT cohort compared with the photon cohort during treatment period	Crude rate. No discussion of competing risk of death	Comparative study of acute toxicities in typical MB demographic (children). Long FU duration. No significant difference in age, sex, MB risk type between cohorts.
Song et al (2014)[32]; Seoul (Korea) 8/9★	Prospective; cohort; enrollment from 2008-2012	– 43 patients with pediatric CNS tumors (13 eligible patients with MB) – Median age of the total sample was 10 y (range, 2-18 y)	Median FU was 22 mo (range, 2-118 mo)	No surgery details; 84% received chemotherapy; passive scatter PT	13 patients treated with photon RT between 2003 and 2012 at the same institution (retrospective)	– Incidence and severity of thrombocytopenia was less severe in PT group cohort compared with photon cohort (P = .012) – Leukocyte and platelet recovery rate significantly greater in PT cohort (P = .003) compared with photon cohort (P = .010) – Diarrhea reported by 23% vs 0% in photon vs PT group (P = .023)	Unclear, likely crude rate	Prospective PT cohort compared with retrospective photon cohort from same institution. Both cohorts had baseline assessment before treatment. Median FU of 22 mo sufficient for outcome of interest. Rare study from Korea.
Hashimoto et al (2019)[33]; Sapporo (Japan) 5/9	Retrospective; comparative; enrollment from 2016-2018	– 17 patients with MB and germ-cell tumors were treated with CSI – 6 patients with MB within the PT cohort; 1 patient with MB within the photon cohort – Median age was 11 y (range, 7-19 y) – 5 average-risk and 2 high-risk patients with MB within the sample	Mean FU: 4 wk	No details about surgery provided; variable chemotherapy; VBS IMPT CSI technique with pencil beam spot scanning	8 patients treated with photons (1 patient with MB within this cohort) at same institution and timeframe	– Both nadir WBC, hemoglobin, and platelet levels and levels 4 wk after CSI were higher in PT than photon group (P < .05), suggesting less myelosuppression for PT – Adolescent and young adults (>15 y) experienced lower incidence of serious acute hematological toxicity when treated with PT compared with photon CSI	Crude rate. No discussion of competing risks	Median FU 4 wk short but may be sufficient for measurement of acute toxicities. WBC, hemoglobin, and platelets were measured at the start and at 4 wk post-CSI. Very small sample size.
Liu et al (2021)[34]; Jacksonville (United States) 4/9	Retrospective; cohort; enrollment from 2008-2020	– 20 adult patients with MB – Median age 27 (range, 22-30 y) – 11 standard-risk and 9 high-risk patients with MB	Median FU 3.1 y (range, 0.6-12.7 y)	Variable (including surgery and chemotherapy); passive scatter + pencil beam scanning PT	No	– No grade 3 or higher acute hematologic toxicities due to CSI – 5/14 patients (36%) had grade 2 leukopenia – Most common grade 2 acute toxicities: anorexia, nausea – OS 95% (95% CI, 72%-99%) – 4-y local control 90% (95% CI, 53%-99%)	Actuarial rate calculated	Small cohort of adult patients with MB. Only 14 patients were included in hematological toxicity analysis (baseline complete blood counts taken). FU duration inadequate for OS but sufficient for acute toxicity.
Suneja et al (2013)[35]; Philadelphia (United States) 3/9	Retrospective; enrollment from 2010-2012	– 48 patients in total (9 patients with MB/PNET) – Median age for all patients was 10.8 y (range, 1-22 y)	No FU after completion of RT	Only 8/48 patients received concurrent chemotherapy; no detailed information about surgery or RT technique	None	– Acute toxicities were CTCAE low-grade and manageable – Toxicities in order of most to least common: dermatitis, alopecia, fatigue, headache, nausea/vomiting and insomnia	Crude rate. No discussion of competing risks	Acute toxicity self-reported. No statement about average FU duration. Baseline acute toxicities were not stated (only stated for weight and Lansky performance. Only 33/48 patients had Lansky performance recorded (all patients appear to be accounted for other acute toxicities).

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Health-related quality of life (n = 4)								
Eaton et al (2020)[36]; Atlanta (United States) 5/9	Mixed; combined patients from 2 prospective trials and a retrospective review with additional patients; enrollment from 2004-2011; multi-institutional	- Cohort of 40 very young patients (<4 y) - 5 eligible patients with MB treated with CSI - Median age for total sample was 2.5 y (range, 3.1-3.9 y)	Median FU: 6.7 y (range, 3-15.4 y)	All patients received chemotherapy; surgery details not specified; RT technique not specified	No control group, but HRQoL scores compared with published cohorts of healthy children (n = 401) and chronically ill patients (n = 367)	- According to both parent and child reports, patients had significantly lower psychosocial, emotional, social, and school-related quality of life scores compared with published healthy children cohort - >one-third of parent-reported HRQoL scores were within a previously defined range for healthy children - HRQoL scores were not significantly different compared with the published cohort of patients with benign chronic health conditions for any of the HRQoL categories - There was no statistically significant association between HRQoL and whether CSI vs involved-field RT was given - 90% of children functioned in a regular classroom, 14 (36%) used a classroom aid, and 18 (46%) had an individualized education plan	Crude rate. No discussion of competing risks	Cohort of very young patients with MB (median age, 2.5 y). The 23-item validated PedsQL tool used to assess both patient-reported and parent-reported HRQoL. Assessments completed at baseline, during treatment, and annually thereafter. 18 patients enrolled prospectively, 22 patients were identified by retrospective review and added to cohort afterward. Median FU of 6.7 y adequate for outcome of interest. Outcomes were self-reported and parent-reported.
Kamran et al (2018)[37]; Boston (United States) 6/9	Prospective; enrollment from 2002-2015	- 116 patients with MB/PNET (108 patients with MB) included in the study - 50 patients with MB/PNET were derived from the Kuhlthau et al (2012)[63] study - Median age of all patients: 7.6 y (range, 2-18 y) - 77 standard-risk and 39 high-risk patients	Median FU: 5 y (range, 1-10.6 y)	PT technique, chemotherapy and surgery not detailed in the study	No control group; findings compared with previously published cohorts of healthy children	- HRQoL was determined through child reports and parent proxy reports according to the PedsQL criteria - Total core score ($P < .001$), physical score ($P < .001$), and psychosocial score ($P = .006$) were low at the time of diagnosis but improved significantly over time for all patients - Total core score, physical score, psychosocial score, and school HRQoL metrics were significantly worse than healthy children ($P < .001$ for all metrics) according to parent proxy reports - Longer FU were associated with greater improvements in HRQoL Only physical score ($P = .024$) was significantly worse than a published cohort of healthy children, according to child report - Socioeconomic status did not appear to affect HRQoL	Crude rate. No discussion of competing risks	Cohort of typical range of patients with MB. Included both self-reported and parent-reported HRQoL (although parent-reported HRQoL missing for some patients). Patients assessed once during first 2 wk of RT, once during last 2 wk, and annually thereafter. Mean FU duration was ~5 y, but not all patients accounted for in FU. Contained 50 patients with MB from the Kuhlthau study (longer FU in this study).
Kuhlthau et al (2012)[38]; Boston (United States) 4/9	Prospective; enrollment from 2004-2010	- 142 patients with MB/PNET - Mean age of all patients: 8.5 y (no range provided)	Average FU interval is unclear	119 patients received definitive surgery; 88 patients received chemotherapy; PT technique was not specified	No	- HRQoL increased significantly over time in patients who received CSI ($P = .0202$) according to PedsQL total core score metric	Crude rate. No discussion of competing risks	Included both self-reported and parent-reported HRQoL, FU duration too short (3 y) and only 43/142 patients available for 3-y FU). Large proportion of patients not accounted for during baseline measurements (106/142)

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Tran et al (2020)[39]; Geneva (Switzerland) 5/9	Retrospective; cohort; enrollment from 1997-2017	- 221 pediatric patients with CNS tumors - 15 patients with MB - No details on age and disease characteristics or number of patients receiving CSI	Median FU was 51 mo (range, 4-222 mo)	No details on surgery/chemotherapy; no details on CSI; pencil beam scanning PT	No	- Cognition/social function scores worsened over time - Family function/global well-being scores improved over time after treatment - 1/15 patients with MB developed grade 3 hearing impairment - OS (5 y) was 64% (95% CI, 38.4%-89.6%) for patients with MB - 5-y disease control was 50% (95% CI, 23.1%-76.9%) for patients with MB	Actuarial rate used for disease control by Kaplan-Meier. Crude rate for HRQoL	Multiple diagnoses; data reported for MB subgroup but no individual patient-level data was available (unclear how many received CSI). HRQoL was assessed (self-reported), but primary outcome was OS. Median FU for entire cohort was 4.12 y.
Brain stem injury (n = 3)								
Gentile et al (2018);[40] Boston (United States) 6/9★	Retrospective; enrollment from 2000-2015	- 216 patients, including 151 eligible patients with MB treated with CSI - Median age of all patients: 6.6 y (range, 0.5-23.1 y)	Median FU of all patients: 4.2 y (range, 0.1-15.3 y)	All patients underwent surgery to various extents; 180 patients (83.3%) treated with chemotherapy; passive scatter PT	No	- 5-y cumulative incidence of brain stem injury was 2.0% (95% CI, 0.7%-4.8%) for all patients - Crude rate of injury was 1.9% (3) for patients with MB - Clinical manifestations of brain stem injury in 3 patients with MB, including ataxia, right-side weakness, quadriplegia, and ventilator dependence - 3- and 5-y OS for total sample was 95% and 87.3%, respectively	Actuarial rate; death defined as competing risk	Multiple diagnoses, 151/216 patients with MB treated with CSI. Individual study data available for patients with brain stem injury, able to reanalyze data for MB population. Median FU of 4.2 y for 198 surviving patients (>90% of cohort), sufficient for outcome of interest.
Giantsoudi et al (2017)[41]; Boston (United States) 6/9★	Mixed; 84 patients enrolled in a prospective trial with remainder of patients studied retrospectively; enrollment from 2002-2011	- 111 patients with MB - Median age: 7 y (range, 32 mo to 22 y) - 76 standard-risk and 35 high-risk patients with MB	Median FU: 4.2 y	Details of surgery not specified; only 4 patients specified to have received chemotherapy; passive scatter PT (avoiding brain stem doses >54 Gy)	No	- 5-y cumulative incidence of symptomatic CNS radiation injury was 4/111 (3.6%), with 3/111 (2.7%) having a grade 3+ injury - 5-y cumulative incidence of brain stem radiation injury or necrosis was 2.7%	Actuarial rate calculation using Gray's test (death defined as competing risk)	Median FU adequate for outcome. Dose and LET distributions were calculated for the treated plans using Monte Carlo system. Relative biological effectiveness values were estimated based on LET-based published models.
Vogel et al (2019)[42]; Philadelphia (United States) 5/9	Prospective; registry; enrollment from 2012-2018	- 166 patients, including 39 patients with MB - Median age of all patients: 10 y (range, 0.5-21 y)	Median FU: 19.6 mo (range, 2-63 mo)	160 patients resected; pencil beam scanning PT	No	- Actuarial incidence of brain stem necrosis was 1/166 (0.7%) at 24 mo (95% CI, 0.1%-5.1%) - The only patient who developed brain stem toxicity was a 12-y-old patient with MB who had been previously treated with twice-daily photon RT (brain stem Dmax 61.2 Gy) and intrathecal methotrexate at a different institution	Actuarial rate by Kaplan-Meier	Prospective registry cohort of multiple diagnoses, small number of patients with MB (39/166). Median FU of 19.6 mo is insufficient for outcome of interest.
Radiation-induced large vessel cerebral vasculopathy (n = 1)								
Kralik et al (2017);[43] Indianapolis (United States) 5/9	Retrospective; enrollment from 2007-2014; endpoint: RLVCLV	- 75 patients, including 25 patients with MB/PNET - Mean age of all patients: 7.9 y (range, 1.5-18 y)	Median FU for all patients: 4.3 y (range, 0.6-9.6 y)	Details of surgery, chemotherapy, and PT technique are not specified	No	- RLVCLV present in 1 (4%) patient with MB, who presented with an acute pontine infarct located in the cerebellum - Time to RLVCLV development in the patient with MB was 7.5 y	Actuarial rate by Kaplan Meier	Multiple diagnoses, 25/75 patients were MB. Individual patient data available for those who developed RLVCLV, data reanalyzed based on this. Individual patient demographic data or subgroup demographic data not available.

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Scoliosis (n = 1)								
MacEwan et al (2017)[44]; Loma Linda (United States) 5/9	Retrospective; case series; enrollment from 2001-2007	- 6 very young patients with MB - Median age at RT was 3.8 y (range, 3.1-5.1 y) - All patients had high-risk MB	Median FU was 13.6 y (range, 8.7-15.8 y)	Maximal safe resection; all patients treated with chemotherapy; PT technique not specified; patients not treated with RT until 3+ y of age)	No	- 2 patients (40%) had scoliosis at FU, with maximum Cobb angles of 36.2° and 19.3° - The remainder of patients had maximum Cobb angles >10° with no evidence of scoliosis - No patients reported chronic back pain or needed spinal surgery at FU - Reduced growth of posterior portions of vertebral bodies observed in all patients; an average posterior to anterior ratio of 0.88 among the 6 patients - Acute effects included hematological toxicity with 3/6 patients requiring packed red blood cell transfusion - 1/6 patients experienced esophagitis - Disease-free survival and OS were 83% at FU - All patients' heights were below the 10th percentile, and all were initiated on growth hormone replacement therapy	No statistical analysis performed	Very small sample size, all patients had high-risk MB. Median FU of 13.6 y adequate. One patient died before clinical/radiographic FU.
Radiation-induced cavernoma (n = 1)								
Trybula et al (2021)[45]; Chicago (United States) 7/9★	Retrospective; cohort; enrollment from 2003-2019; endpoint: RT-induced CM	- 79 patients with MB, including 49 patients treated with PT and 30 patients treated with photon therapy - Mean age was 8.6 y for the PT cohort and 8.9 y for the photon therapy cohort (total sample range, 3.2-18.3 y)	Mean FU for the PT cohort was 56.8 mo and 105 mo for the photon therapy cohort	All patients surgically resected for primary tumor; all patients treated with chemotherapy; PT technique not specified	30 patients treated with photon RT in the same timeframe at the same institution	- 26 patients (86.7%) treated with photon RT and 42 patients (85.7%) treated with PT developed postradiation CMs. - Average time to CM development was shorter in the PT cohort compared with the photon cohort (18.2 vs 40.2 mo; P = 1.98e-4)	Actuarial rate by Kaplan-Meier	Similar demographics (age, treatment) between proton and photon cohort. Baseline pretreatment MRI was done in all patient assessments for CM. Median FU of 7.2 y sufficient for outcome of interest.
Permanent alopecia (n = 1)								
Min et al (2014)[46]; Boston (United States) 4/9	Unclear study design and years of enrollment	- 12 patients with MB - Median age was 6 y (range, 4-15 y) - 5 standard-risk and 7 high-risk patients	FU was >1.25 y	No surgical details; all patients received either conventional dose or high-dose chemotherapy; passive scatter PT	No	- 9 patients (75%) had permanent alopecia; 7 patients (58%) had grade 2 permanent alopecia - All high-risk patients with MB showed either grade 1 or 2 permanent alopecia - 2/5 standard-risk patients with MB had grade 1 or 2 permanent alopecia	Crude rate. No discussion of competing risks	Unclear study design, unclear y of enrollment and small sample size. Duration of FU likely too short for assessment of permanent alopecia.

*Abbreviations:*3DCPT = 3-dimentional conformal proton therapy; 3DCRT = 3-dimentional conformal radiation therapy; CI = confidence interval; CM = cavernous malformation; CMS = cerebellar mutism syndrome; CNS = central nervous system; CSI = craniospinal irradiation; CTCAE = Common Terminology Criteria for Adverse Events; EFS = event-free survival; FSIQ = full-scale intelligence quotient; FU = follow-up; GTR = gross total resection; HR = hazard ratio; HRQoL = health-related quality of life; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; IQR = interquartile range; KP = Kaplan-Meier; LET = linear energy transfer; LF = local failure; MGH = Massachusetts General Hospital; MB = medulloblastoma; MRI = magnetic resonance imaging; NOS = Newcastle Ottawa Scale; OS = overall survival; PFS = progression-free survival; PT = proton radiotherapy; RT = radiation therapy; RFS = recurrence-free survival; RLVCLV = radiation-induced large vessel cerebral vasculopathy; SD = standard deviation; SPNET = supratentorial primitive neuroectodermal tumor; STR = subtotal resection; VBS = vertebral body sparing; WBC = white blood cell.

* Studies are reported only once in this table. Studies that report on multiple outcome categories are listed under their primary endpoint.

★ Indicates "high-quality" studies in the column (comparative study; NOS score ≥6) that were most influential in forming the conclusions of this systematic review. See Supplementary E4 for detailed information on how NOS scores for each study were assigned.

including growth hormone deficiency, adrenal insufficiency, and precocious puberty were comparable between the 2 radiation modalities.

Late ototoxicity

Three studies reported on ototoxicity, including 1 prospective single-arm trial (NOS, 6 out of 9) and a comparative cohort study (NOS, 8 out of 9). The ototoxicity rates in the prospective study (16% at 5 years) appeared to be less than referenced historic published cohorts (24% in COG A9961 cohort of standard-risk MB).[47] In the comparative cohort study, patients treated with PT and photons had similar grade 3 and 4 ototoxicity, despite lower mean cochlear dose, lower mean cisplatin dose, greater proportion of tumor-bed boost alone, and routine use of amifostine in patients treated with PT. Thus, the existing clinical evidence base is conflicting as to potential lower ototoxicity rates with PT.

Acute toxicities

Six studies reported on acute toxicities of patients treated with proton CSI, 2 of which scored ≥8 out of 9 on the NOS. Two of the 6 studies reported on an adult population (median age in the late 20s).[30,34] Patients undergoing PT CSI had reduced incidence, severity, and faster recovery of acute hematological toxicities, including thrombocytopenia, leukopenia/lymphopenia, and anemia compared with patients treated with photon CSI.[30,34] Patients treated with PT also reported almost 5 times less weight loss (1.2% vs 5.8%; $P = .004$) and fewer patients had significant (defined as >5% baseline) weight loss (16% vs 64%; $P = .004$).[30] This was likely attributed to less grade 2 nausea and vomiting (26% vs 71%) and far lower rates of esophagitis requiring medical management (5% vs 57%; $P < .001$).[30] Patients treated with PT also had lower incidence of diarrhea (0% vs 23%; $P = .023$). This was observed for both vertebral body sparing (VBS) CSI and non-VBS CSI.

Health-related quality of life

There were 4 studies that reported on health-related quality of life (HRQoL) for patients treated with PT, with follow-up ranging from 4.25 to 6.7 years, though it was difficult to draw conclusions as there were no direct comparisons between PT and photon cohorts. Studies used the validated PedsQL score and often included both child reports and parent-proxy reports. Two studies compared findings to published cohorts of healthy children, and 1 study found that QoL scores were not significantly different compared with a published cohort of patients with benign chronic health conditions. None of the studies in this category scored ≥8 out of 9 on the NOS.

Brain stem injury

Three studies (with median follow-up ranging from 4-5 years) reported on the incidence of CNS radiation injury and brain stem injury in patients treated with PT CSI. The reported 5-year cumulative incidences (2.0%-3.6%) were comparable to previously reported incidences of CNS and brain stem radiation injury from photon RT.[48,49] There were no studies with a comparative photon cohort in this category.

Radiation-induced cavernoma

A comparative retrospective review of 79 patients with MB (NOS, 7 out of 9) with follow-up of 4.75 years found that those treated with proton CSI had shorter average time to develop cavernous malformations (18.2 vs 40.2 months) compared with photons. However, it was reassuring that the frequency of developing cavernomas requiring surgical resection/intervention did not differ between proton and photon cohorts. The clinical significance of this is yet to be established.

Other outcomes

One study reported rates of permanent alopecia in patients treated with PT (75% with permanent alopecia; 58% with grade 2 permanent alopecia) at a median follow-up duration of just over 1.25 years.[46] A small retrospective case series (median follow-up, 13.6 years) reported on the effect of VBS PT on spine outcomes of young patients with MB, finding that 2 patients (40%) had scoliosis at follow-up; however, none reported chronic back pain or required spinal surgery.[44] Another retrospective study reported on the incidence of radiation-induced large vessel cerebral vasculopathy in pediatric patients with CNS tumors treated with PT, finding that only 1 out of 25 treated patients developed radiation-induced large vessel cerebral vasculopathy at a median follow-up of 4.3 years. These studies generally had small sample sizes and were not comparative, limiting generalizability of these findings.

Discussion

To our knowledge, this is the largest systematic review to date of published clinical outcomes of PT for patients with MB. The highest quality studies were well-designed comparative cohort studies (using either prospective or retrospective data), with adequate follow-up time for the outcomes of interest. With 9 studies being scored 8 or greater (out of 9) on the NOS, we felt there was overall "moderate" GRADE clinical evidence that supports favorable disease outcomes and toxicity profiles for PT.

Our systematic search did not identify any randomized controlled trials, which was expected due to the rarity of the disease. At this point, with general consensus in the pediatric oncology community that PT is superior to that of photon-based craniospinal treatment, it is unlikely that there will be therapeutic equipoise required for future randomized controlled trials to be ethically conducted. The most robust studies in our review were comparative matched modern cohorts, prospectively recorded in parallel over the same period. This allowed for comparison of PT with modern photon techniques and ensured consistent diagnostic, staging, and treatment practices across both cohorts. For example, Kahalley et al compared cohorts from the Hospital for Sick Children in Toronto, Canada, and Texas Children's Hospital, where photon and proton were standard of care, respectively[12]—this helped ensure that the choice of PT was not due to potential confounders such as differences in other disease management over time. Another often-used methodology was the comparison of cohorts in different periods at the same institution. For example, Paulino et al compared 2 cohorts treated at Texas Children's Hospital from 1996 to 2006 and 2006 to 2014, respectively, when each technique was the standard of care.[12] This ensured that the population of patients treated in each cohort would be similar demographically, but this approach was more open to possible confounders in terms of differences in chemotherapy regimens and RT technique. Regardless, the timeframes were close enough that there were likely no major paradigm changes in the management of MB during those respective years.

Disease control

Previously, there were concerns that PT may have worse disease outcomes as a result of improper relative biological effectiveness weighting, differences in dose distributions, or possible higher than expected relapse rates in the spine.[50] In this review, 2 robust comparative cohort studies[12,13] with >5 years of follow-up found no differences in OS, progression-free survival, and patterns of failure between patients treated with PT and photon therapy.[13] These cohorts were matched on demographic, prognostic, and treatment variables as known at the time. In addition, a proton-only cohort from MGH with a 9.3-year median follow-up found 10-year OS rates of 79.3% for the entire cohort, 86.9% for standard risk, and 68.9% for intermediate-to-high risk. These numbers are similar to disease control outcomes published in photon trials COG A9961, St. Jude Medulloblastoma-96, and the more modern ACNS0331.[14]

Secondary malignancy

Another concern of PT is that neutron scatter could increase total body dose and may possibly increase the risk of secondary malignancies such as leukemia.[51,52] Though no study was powered to detect differences in secondary malignancy rates, it should be noted that out of 2 comparative studies (with median follow-ups from 6.2 to 8.7 years) reported on secondary malignancies, both found the proton cohort to have numerically lower secondary malignancy rates compared with photons (0%-4.9% vs 7%-8%).[12,13] Neither finding was statistically significant. Though solid secondary malignancies can occur decades after initial exposure, the median time to secondary tumor in children treated with MB is 5.8 years in photon trials.[53] In addition, hematologic secondary malignancies typically occur within a few years; therefore, it was reassuring that no secondary leukemias were detected in the proton cohorts. Another single-cohort study with a 9.3-year median follow-up found the 10-year cumulative incidence of secondary malignancy was 2.1% (95% confidence interval [CI], 0.6-5.8) for patients treated with PT.[14] This number appears to be lower than the estimated cumulative 10-year secondary malignancy rate of 4.2% (95% CI, 1.9-6.5) in the photon COG A9961 trial, which had a median follow-up of 9.7 years (range, 0.2-13.7).[53] These findings corroborate with toxicity and risk modeling studies, which predict lower secondary malignancy rates for patients treated with PT[54,55] based on the smaller volume of normal tissue irradiated in anterior exit regions. A recent National Cancer Database study also supports these results, finding that in general, PT led to significantly lower risk of secondary malignancy compared with photon intensity modulated RT and 3-dimensional conformal RT,[56] though the study was limited by a median follow-up of 5.1 years and a relatively low number of patients receiving PT (1.3%).[57] In contrast, a study recently presented at the American Society for Radiation Oncology and the International Symposium on Pediatric Neuro-Oncology with a 6-year median follow-up found no differences in secondary malignancy rates between children with primary CNS tumors treated with protons and photon intensity modulated RT.[58] However, only a minority of patients in this study received CSI, and patients treated with PT in that study were significantly younger (8.4 vs 10.4 years; young age of treatment may be associated with higher rates of secondary malignancy). Characterization of rates of second malignancy with large cohorts and longer follow-up are necessary to better understand the rates of second malignancy associated with PT craniospinal radiation.

Neurocognitive outcomes

In terms of other toxicities, the evidence was most robust for superior neurocognitive outcomes associated with PT. Superior intellectual outcomes for PT was demonstrated in 5 studies, including 2 comparative studies with case-matched cohorts based on disease, treatment,

and patient factors such as parental education, baseline IQ scores, and socioeconomic status.[18,19] The studies found that patients treated with PT had, on average, higher IQ scores by 1 SD, along with better verbal comprehension and perceptual reasoning scores. With average follow-up lengths of 4 to 5 years, patients treated with photons were found to decline in global IQ by a statistically significant 0.9 points per year on average ($P = .009$) and 2.2 points in working memory per year ($P = .001$), whereas patients treated with PT showed stable IQ and working memory.[18,19] The magnitude of these differences are quite significant, and many clinicians may argue that PT should be recommended on this basis alone due to the detriment of neurocognitive decline on patients' long-term QoL. It was notable, in both studies, that processing speeds declined equally in both cohorts. This may be attributable to the frontal lobes in both cohorts receiving similar doses of radiation from the whole brain component of CSI. Poor cognitive outcomes were also correlated with younger age at radiation (<7 years of age) and presence of posterior fossa syndrome adverse factors also seen with photon craniospinal RT.

Endocrinopathy

PT was associated with significantly lower incidence of hypothyroidism (23% vs 69%; $P = .001$), sex hormone deficiency (3% vs 19%; $P = .025$), and greater heights (mean ± SD, -1.19 ± 1.22 vs -2 ± 1.35; $P = .02$) at follow-up.[23] Further studies showed lower incidences of both central and peripheral hypothyroidism, which suggest that both the thyroid gland and pituitary were able to be spared with PT.[25] On the other hand, incidences of growth hormone deficiency, adrenal insufficiency, and precocious puberty were not found to differ between photon and proton cohorts.[24] This is likely due to the relative sensitivity of growth hormone and ACTH-producing pituitary tissue to radiation, which meant that even low doses were enough to cause lasting damage. An additional study by Yip et al (published outside the timeframe of our review) has reported similar findings: patients treated with PT had lower odds of hypothyroidism (17% vs 49%) and possible sex hormone deficiency (0% vs 17%); however, they were not spared from growth hormone deficiency compared with patients treated with photon therapy.[59]

Late ototoxicity

An early retrospective study by Moeller et al in 2011[29] and Yock et al's[28] prospective single-arm trial both showed low rates of grade 3 to 4 hearing loss with PT compared with our referenced historical photon-based trial, COG A9961.[47] However, this difference might be due to the longer median follow-up in COG A9961 (8.9 years) compared with the PT studies (11 months and 5.2 years, respectively).[28] When similar photon and proton cohorts were compared in Paulino et al, grade 3 to 4 ototoxicity rates were similar regardless of treatment modality, despite the proton cohort having lower cochlear dose, lower mean cisplatin dose, and routine use of amifostine as a radioprotector—all of which were factors that may predict lower ototoxicity.[27] As Paulino et al is the most robust study on ototoxicity (NOS, 8 out of 9), the current evidence suggests PT likely has comparable rates of ototoxicity compared with photon therapy for patients with MB. Hearing loss is affected by both RT and chemotherapy, which is also titrated to measured changes in audiogram during treatment, so perhaps there are too many factors for a change in radiation modality to effect a clinically significant decrease in ototoxicity. More studies are required.

Acute toxicities

There was robust evidence that patients treated with protons had significantly less acute toxicities, including reduced myelosuppression, lower rates of grade 3 esophagitis (5% vs 57%), diarrhea, lost 5 times less weight (1.2% vs 5.8%), and endured less nausea/vomiting (26% vs 71%). High quality studies existed for both adult and children with MB. Consideration of acute toxicities is especially important for the adult population, as they often have a difficult time completing the CSI component of treatment due to myelosuppression, weight loss, and other acute toxicities.

Health-related quality of life

It stands to reason that with less late toxicity, patients would also report better HRQoL after treatment with PT. However, there were no comparative studies in this domain, and HRQoL outcomes reported among patients were highly variable. Kamran et al and Eaton et al both reported PedsQL scores for patients treated with protons, finding that HRQoL was on average similar to a control cohort of children with benign chronic health conditions.[36,37] Unfortunately, there are no historical photon-treated MB cohorts that report on PedsQL scores to allow for comparison. The modern ACNS0331 trial did record PedsQL for patients treated with photons, which will allow future comparison of the cohorts once those findings are reported. Further multi-institution collaboration with standardized collection and pooling of HRQoL data, as spearheaded by the Pediatric Proton/Photon Consortium Registry, will also allow for more insight into the QoL of patients with MB treated with PT. Since our original review, Doig et al also conducted a systematic review

on HRQoL for survivors of proton-treated childhood cancer, concluding that at the current moment, there is insufficient quality evidence to compare HRQoL outcomes between the 2 modalities.[60]

Brain stem injury

The initial series of PT for other pediatric CNS cancers reported broader ranges of brain stem injury (0%-16%) compared with photon therapy (2.2%-8.6%)[40,61]; therefore, it was theorized that if there were high linear energy transfer regions from PT within the brain stem leading to higher relative biological effectiveness than estimated by treatment planning systems, then this could possibly lead to higher rates of brain stem injury for patients treated with protons. This was not demonstrated in any of the 3 studies included on this matter. Rates of brain stem radiation injury were low (2.0%-3.6% 5-year cumulative incidence).[17,40,42] The reported data suggest that there should be no difference in brain stem toxicity between patients treated with protons and photons, provided that dose constraints are met.

Radiation-induced cavernoma

It is not yet understood why PT may lead to higher incidences of radiation cavernomas; however, it has been observed in other pediatric CNS cancers that PT may lead to higher rates of pseudoprogression[62] or cerebral microbleeds,[43] both of which are also thought to be radiation-induced vascular damage. There is possibly a difference in the vascular biology of patients treated with PT in both the acute and chronic phase that leads to these differences.

Strengths

To our knowledge, this is the most comprehensive systematic review of the clinical outcomes of patients with MB treated with PT. Compared with prior reviews, we have identified more relevant studies and overall report longer follow-ups (average of 5 years). A strength of our study is the quality appraisal methodology. Because only nonrandomized studies were identified, we applied the NOS to estimate study quality based on individual study design, selection of study groups, comparability, follow-up duration, and ascertainment of outcomes rather than grading broadly based on the type of study.[10] Sample size was not a distinct factor in NOS scoring; therefore, we also considered that when deciding which studies were most informative (Table 3; see studies marked with a dagger symbol). To ensure reliability of scores, we used 2 independent assessors for scoring (S.Y., K.P.) and resolved discrepancies by consensus.

Limitations

One of the limitations in this systematic review is the heavy reliance on 1 institution (MGH) for half of the studies (n = 17). Altogether, the studies reported a total of 2059 patients. When reviewed carefully, we conservatively estimated only 630 to 654 unique patients, as several papers used the same or overlapping cohorts from one institution (Supplementary E5). Another limitation is the lack of molecular subgrouping information in any studies, now known as an important prognostic factor.[3] This is especially important when comparing disease control outcomes, and we can only assume that there is likely a comparable distribution of molecular subtypes between the cohorts. However, it is reassuring that event-free and OS rates reported in both proton and photon studies were comparable to those reported in the literature such as COG A9961 phase 3 study, St. Jude Medulloblastoma-96 study, and the more modern ACNS0331 trial.[2–4] Therefore, even without matching using molecular subgrouping, we are fairly confident that patients treated with PT have no differences in disease control outcomes compared with patients treated with photon therapy.

Another limitation is the variability in the statistical methodology used to calculate cumulative incidences and report on other toxicity endpoints (Table 3). This limits the comparability of the incidences between studies that use different methodology. The majority of studies[19] use crude rates in calculating incidences. Fifteen studies describe actuarial rates (typically Kaplan-Meier estimate), while only 4 of those studies account for the competing risks of death using more rigorous methodology (ie, Fine-Gray methods). Crude rates may be misleading if the incidences of toxicities are calculated based on the initial cohort size.

Future directions

Studying late toxicities of a rare childhood cancer is challenging and especially difficult when doing so for a new, yet-to-be widely accessible technology. Most studies focused on 1 or 2 toxicities, and as such there are many late toxicities yet to be studied. These gaps of knowledge are opportunities for future research. These include height, permanent alopecia, gonadal/fertility issues, visual disturbances, cataracts, osteoradionecrosis, xerostomia, cerebrovascular complications (stroke, transient ischemic attacks, aneurysm), and cardiovascular disease.[63,64] The reason some of these have not been reported are due to the long follow-up times required to accurately assess risk and incidence. For example, occlusive cerebrovascular

disease such as strokes and transient ischemic attacks tend to develop 20 to 25 years after CSI, whereas aneurysms can develop over 30 years after treatment.[64,65] Cardiovascular disease is also difficult to study as the risk of cardiac mortality increases substantially after 25 to 30 years[66] based on data from other childhood cancers. Other late toxicities are relatively uncommon not routinely studied, including ataxia, facial nerve palsies, mineralizing microangiopathy, refractory seizures, and respiratory disorders.

Future studies should also report actuarial rates of toxicities instead of crude rates, preferably using Fine-Gray or other methods that account for the competing risks of treatment failure and death. Additionally, we restricted our analysis to patients with MB as the clinical situation where craniospinal radiation is routinely incorporated into treatment. Other pediatric CNS tumors that have a propensity for leptomeningeal dissemination may require craniospinal radiation, and therefore could also potentially benefit from PT. It is reasonable to assume the benefits of PT would extend to other clinical scenarios including craniospinal radiation, and further characterization of PT outcomes in these less common patient populations is warranted.

Conclusion

In this systematic review, we show that there is moderate grade clinical evidence supporting PT as the preferred delivery technique for both children and adults with MB requiring craniospinal RT, largely on the basis of superior intellectual outcomes, decreased hypothyroidism, and improved acute toxicities while maintaining comparable disease control. Assessment of long-term benefits of PT will requiring ongoing follow-up, ideally through prospective studies or high-quality longitudinal registry studies.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101189.

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