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Clinical outcomes of medulloblastoma patients treated with proton radiotherapy: a systematic review

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Short Title: Clinical outcomes of medulloblastoma patients treated with proton radiotherapy: a systematic review

Abstract

Purpose:

The aim of this study was to comprehensively review all studies examining clinical outcomes of craniospinal irradiation with proton beam therapy for medulloblastoma, to determine whether theoretical dosimetric advantages have translated into superior clinical outcomes, including survival and toxicities compared to traditional photon based techniques.

Methods:

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

Results:

Thirty-five studies were included, with a total of 2059 patients reported (representing an estimated 630 to 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 of 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, SD 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 (10-

yr) (85.3-86.9% for standard-risk disease), progression-free survival (10-yr), brainstem injury and other endocrine outcomes were similar to those reported for photon therapy. There was insufficient evidence to make conclusions on endpoints of quality of life, ototoxicity, secondary malignancy, alopecia, scoliosis, carvernomas or cerebral vasculopathy.

Conclusions:

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

Introduction

Medulloblastoma (MB) is an embryonal central nervous system (CNS) tumour located in the posterior cranial fossa. It is the most common malignant brain tumour in children, comprising nearly 20% of all paediatric brain tumours. The annual incidence in the United States is approximately 350-450 patients per year (1). Though adults can have medulloblastoma as well, paediatric incidence is ten-fold higher with peak incidence occurring in children aged 4 to 9 years old.

MB comprises a biologically heterogenous group of tumours 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 non-infants (over 3 years of age). Treatment outcomes are associated with patient age as well as clinicopathological and molecular factors. Five-year overall survival rates for standard risk MB (defined as patients >3 years old with gross total resection and no evidence of metastases) is 70-85% (2–5). On the other hand, patients with a subtotal resection, metastasis at diagnosis, or those that are <3 years old are considered to be high risk, and have 5-year overall survival rates of <70% (2–5). Contemporary studies have defined prognostic molecular factors (5) which will

guide treatment in the future. However, most of the existing body of literature continues to make reference to standard and high-risk stratification.

Craniospinal irradiation (CSI) with a radiotherapy boost to the tumor bed is an essential component of standard of care treatment for children of sufficient age after resection of tumour, although infants may require radiotherapy delay strategies to mitigate long-term toxicities. 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 therapy (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 medulloblastoma with the aim of reducing late toxicities in patients. Significant capital and operating costs associated with proton therapy limit its availability worldwide (6,7) and access to the therapeutic benefits of proton beam radiotherapy in pediatric populations are a key driver of investment in proton beam therapy (8).

Thus far, studies demonstrating superiority of proton therapy have mostly been dosimetric comparisons and clinical outcome data has been limited. A systematic review of proton therapy for all pediatric CNS tumours published in 2016 only found 3 case series on clinical outcomes of medulloblastoma patients (9). They concluded that there was not enough clinical evidence to support or refute superiority of proton therapy at the time (9). In the last six years, additional clinical data has begun to emerge and we sought to systematically re-examine this question: Does proton therapy for adjuvant craniospinal irradiation of medulloblastoma patients result in improved clinical outcomes and toxicities profiles?

The aim of this study is to provide a comprehensive systematic review of all studies examining clinical outcomes of proton therapy for craniospinal irradiation as adjuvant therapy following resection of medulloblastomas in both adults and children. This paper should benefit radiation oncologists, pediatric neuro-

oncologists, physicists and healthcare system funding bodies by compiling the data into one source and assessing the quality of the existing body of evidence that examines the benefit of proton beam therapy for medulloblastoma and other malignancies that require CSI.

Methods/Literature Search

We performed a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Figure 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 pre-defined inclusion and exclusion criteria.

Search strategy

A systematic search for scientific literature on proton therapy for patients with medulloblastoma was carried out in 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 (GB). 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 1.

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 modelling studies, animal studies, descriptive or narrative studies, feasibility assessments, cost-effectiveness analyses, letters, news reports, editorials, reviews, notes or conference abstracts.

Two authors independently reviewed all titles and abstracts for eligibility using Covidence software (Melbourne, Australia); discrepancies were resolved either by consensus or approaching a third researcher for adjudication. Two researchers also independently conducted full text review using the following PICO eligibility criteria (Table 1):

Participants

Patients must have pathological diagnoses of medulloblastoma. Supratentorial primitive neuroectodermal tumour (SPNET) 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 medulloblastoma and information of follow-up and outcomes were available for this subgroup of patients (either reported as a medulloblastoma group or reported for individual patients.)

Interventions

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

Comparators

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 radiotherapy treatment techniques, no chemotherapy (or pre-modern regimens), older surgical techniques, and different patient risk classifications. As such, it would have been difficult to draw meaningful toxicity comparisons with proton therapy from the modern era. Instead, we

compare toxicity and disease control outcomes with 3 modern-era benchmark photon trials: COG A9961 Phase III study, St. Jude Medulloblastoma-96 study and the more recent ACNS0331 trial.

Outcomes

We only included studies that reported clinical endpoints. We included all clinical endpoints reported, 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 two possibly relevant titles in other languages, which are provided in Supplementary 2.

Data extraction

Data was extracted in duplicate by two independent investigators (SY/KP) and data uploaded onto Microsoft Excel. 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 (10) (Supplementary 3). To ensure reliability of scores, 2 independent assessors (SY/KP) assigned scores and discrepancies were resolved by consensus. A maximum of 4 points were given based on selection of the proton and photon cohorts, 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 (Figure 1), with a total 2059 patients reported (representing an estimated 630 to 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 that were not included in the first publication (Supplementary 5). 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. 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 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, SD 1.6). Nine studies scored ≥8 out of 9 on the NOS (Table 3, Supplementary 4). 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 below.

Disease control and secondary malignancies:

Thirteen studies reported on disease control outcomes and it was 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 proton-treated patients from MGH with a median follow-up of 9.3 years. The other 2 studies were matched cohort studies with >5 years follow-up in both proton and photon cohorts, and both scored ≥8 out of 9 on the NOS. Overall survival (up to 10-yr), progression-free survival (up to 10-yr) and patterns of failure were comparable between these series. Ten-year OS ranged from 85.3-86.9% for standard-risk MB patients 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 two studies comparing photons and protons, but did not reach statistical significance in any individual study.

Neurocognitive outcomes:

Two matched cohort studies demonstrated superior cognitive outcomes in patients treated with PT compared to 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=0.009) and 2.2 points in working memory per year (P=0.001) on average (12). In addition, patients also had better perceptual reasoning outcomes and verbal comprehension after PT versus photons. Processing speed declined similarly in PT and photon-treated patients in both studies.

Endocrinopathy:

Four studies reported on endocrine results; one 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=0.001) . 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=0.025) and greater heights (mean ± SD: -1.19 ± 1.22 vs -2 ± 1.35; p = 0.02) at follow up. The incidence of other endocrinopathies, including growth hormone deficiency, adrenal insufficiency and precocious puberty were comparable between the two radiation modalities in series comparing the two.

Late Ototoxicity:

Three studies reported on ototoxicity, including one prospective single arm trial (NOS 6/9) and a comparative cohort study (NOS 8/9). 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) (13). 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 toxicity:

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 six studies reported on an adult population (median age in the late 20s) (14,15). Patients undergoing PT CSI had reduced incidence, severity, and faster recovery of acute hematological toxicities, including thrombocytopenia, leukopenia/lymphopenia and anemia compared to patients treated with photon CSI (14,16). Patients treated with PT also reported almost five-fold less weight loss (1.2% vs 5.8%, p=0.004) and fewer patients had significant (defined as >5% baseline) weight loss (16% vs 64%, p=0.004) (15). 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<0.001) (15). Patients treated with PT also had lower incidence of diarrhea (0% vs 23%, p=0.023). This was observed for both vertebral-body-sparing CSI and non-VBS CSI.

Health-related Quality of life:

There were 4 studies that reported on QoL for PT-treated patients 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 one 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.

Brainstem Injury:

Three studies (with median follow-up ranging from 4-5 years) reported on the incidence of CNS radiation injury and brainstem 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 brainstem radiation injury from photon RT (17,18) There were no studies with a comparative photon cohort in this category.

Radiation-induced cavernoma

A comparative retrospective review of 79 medulloblastoma patients (NOS 7/9) with follow up of 4.75 years found that those treated with proton CSI had shorter average time to develop cavernous malformations (18.2 mo vs 40.2 mo) compared to 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 proton-treated patients (75% with permanent alopecia; 58% with gr.2 permanent alopecia) at a median follow-up duration of just over 1.25 years (21). A small retrospective case series (median follow-up 13.6 years) reported on the effect of vertebral-body sparing PT on spine outcomes of young MB patients, finding that 2 patients (40%) had scoliosis at follow-up, however none reported chronic back pain or required spinal surgery (22). Another retrospective study reported on the incidence of radiation-induced large vessel cerebral vasculopathy (RLVCLV) in proton-treated pediatric CNS patients, finding only one out of twenty-five patients treated developed RLVCLV 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 proton therapy for patients with medulloblastoma. 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 proton therapy 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 time period. This allowed for comparison of proton therapy 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 and Texas Children's Hospital, where photon and proton were standard of care respectively (12) – this helped ensure that the choice of proton therapy 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 time-periods at the same institution. For example, Paulino et al. compared two cohorts treated at Texas Children's Hospital from 1996-2006 and 2006-2014 respectively, when each technique was the standard of care (23). 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 radiotherapy technique. Regardless, the time-frames were close enough that there were likely no major paradigm changes in the management of medulloblastoma during those respective years.

Disease control

Previously, there concerns that proton therapy may have worse disease outcomes as a result of improper RBE weighting, differences in dose distributions, or possible higher than expected relapse rates in the spine (24). In this review, two robust comparative cohort studies(23,25) with > 5 years follow-up found no differences in overall survival, recurrence free survival and patterns of failure between patients treated with proton and photon therapy (25). These cohorts were matched on demographic, prognostic, and treatment variables as known at the time. In addition, a proton-only cohort from MGH with 9.3 years median follow-up

found 10-year OS rates of 79.3% for entire cohort; 86.9% for standard risk; 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 (26).

Secondary malignancy

Another concern of proton therapy is that neutron scatter could increase total body dose and may possibly increase the risk of secondary malignancies such as leukemia (27,28). 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 to photons (0-4.9% versus 7-8%) (23,25). 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 medulloblastoma is 5.8 years in photon trials (29) In addition, hematologic secondary malignancies typically occur within a few years, and therefore it was reassuring that no secondary leukemias were detected in the proton-cohorts. Another single cohort study with 9.3 year median follow-up found the 10-year cumulative incidence of secondary malignancy was 2.1% (95% CI: 0.6-5.8) for proton-treated patients(26). 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) (29). These findings corroborate with toxicity and risk modelling studies, which predict lower secondary malignancy rates for patients treated with proton therapy (30,31) 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, proton beam therapy led to significantly lower risk of secondary malignancy compared with photon IMRT and 3DCRT (32), though the study was limited by a median follow-up of 5.1 years, and a relatively low number of patients receiving proton therapy (1.3%) (33). In contrast, a study recently presented at ASTRO and ISPNO with 6 year median follow-up found no differences in secondary malignancy rates between children with primary CNS tumours treated with protons and photon IMRT therapy (34). However, only a minority of patients in this study received CSI and proton-treated patients in that study were significantly younger (8.4 vs 10.4 yrs) (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 proton beam therapy. Superior intellectual outcomes for proton therapy was demonstrated in 5 studies, including 2 comparative studies with case-matched cohorts on the basis of disease factors, treatment factors, and patient factors such as parental education, baseline IQ scores, and socioeconomic status (12,33). The studies found that proton-treated patients had, on average, higher IQ scores by one standard-deviation, along with better verbal comprehension and perceptual reasoning scores. With average follow up lengths of 4 to 5 years, photon-treated patients were found to decline in global IQ by a statistically significant 0.9 points per year on average (P=0.009) and 2.2 points in working memory per year (P=0.001), whereas proton-treated patients showed stable IQ and working memory (12,33). The magnitude of these differences are quite significant and many clinicians may argue that proton therapy should be recommended on this basis alone due to the detriment of neurocognitive decline on patients' quality of life long-term. 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 (less than 7 years old) and presence of posterior fossa syndrome adverse factors also seen with photon craniospinal radiotherapy.

Endocrinopathy

Proton therapy was associated with significantly lower incidence of hypothyroidism (23% vs 69%, p=0.001), sex hormone deficiency (3% vs 19%, p=0.025) and greater heights (Mean ± SD: -1.19 ± 1.22 vs -2 ± 1.35; p = 0.02) at follow up (34). 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 proton therapy (35). On the other hand, incidences of GH deficiency, adrenal insufficiency and precocious puberty were not found to differ between photon and proton cohorts (36). This is likely due to the relative sensitivity of

GH 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 proton therapy had lower odds of hypothyroidism (17% versus 49%) and possibly sex hormone deficiency (0% versus 17%); however they were not spared from growth-hormone deficiency compared to photon-treated patients (37).

Late Ototoxicity

An early retrospective study by Moeller et al. in 2011 (38) and Yock et. al's prospective single arm trial (32) both showed low rates of grade 3/4 hearing loss with PT compared to our referenced historical photon-based trial COG A9961 (13). However, this difference might be due to the longer median follow-up in COG A9961 (8.9 years) compared to the PT studies (11 months and 5.2 years respectively) (39). When similar photon and proton cohorts were compared in Paulino *et al.*, grade 3-4 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 (40). As Paulino *et al.* is the most robust study on ototoxicity (NOS score 8/9), the current evidence suggests PT likely has comparable rates of ototoxicity compared to photon therapy for patients with medulloblastoma. Hearing loss is impacted by both radiation 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 gr.3 esophagitis (5% vs 57%), diarrhea, lost 5x 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 medulloblastoma. Consideration of acute toxicities is especially important for the adult population, as they often have a difficult time completing the craniospinal irradiation component of treatment due to myelosuppression, weight loss and other acute toxicities.

Health-related quality of life (HRQoL)

It would reason that with less late toxicity, patients would also report better health-related quality of life after treatment with proton therapy. However, there were no comparative studies in this domain and health-related quality of life (HRQoL) outcomes reported amongst patients were highly variable. Kamran et al. and Eaton et al. both reported PedsQL scores for patients treated with protons, finding that HQRoL was on average similar to a control cohort of children with benign chronic health conditions. Unfortunately, there are no historical photon-treated medulloblastoma 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 (PPCR), will also allow for more insight into the quality of life of medulloblastoma patients treated with proton therapy. Since our original review, Doig et al. also conducted a systematic review on health-related quality of life for proton-treated childhood cancer survivors, concluding that at the current moment, there is insufficient quality evidence to compare HRQoL outcomes between the two modalities (41).

Brainstem Injury:

The initial series of proton therapy for other pediatric CNS cancers reported broader ranges of brainstem injury (0 to 16%) compared with photon therapy (2.2-8.6%) (42,43), therefore it was theorized that if there were high linear energy transfer (LET) regions from proton therapy within the brainstem leading to higher relative biological effectiveness (RBE) than estimated by treatment planning systems, then this could possibly lead to higher rates of brainstem injury for patients treated with protons. This was not demonstrated in any of the three studies included on this matter. Rates of brainstem radiation injury were low (2.0-3.6% 5-year cumulative incidence) (42,44,45). The reported data suggests that there should be no difference in brainstem toxicity between proton and photon-treated patients provided that dose constraints are met.

Radiation-induced cavernoma

It is not yet understood why proton therapy may lead to higher incidences of radiation cavernomas, however it has been observed in other pediatric CNS cancers that proton therapy may lead to higher rates of pseudoprogression (46) or cerebral microbleeds (47), both of which are also thought to be

induced by radiation-induced vascular damage. There is possibly a difference in the vascular biology of proton-treated patients 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 medulloblastoma patients treated with proton therapy. Compared to prior reviews, we have identified more relevant studies and overall report longer follow ups (average 5 years). A strength of our study is the quality appraisal methodology. Since 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 "starred" studies). To ensure reliability of scores, we utilized 2 independent assessors for scoring (SY/KP) and where there were discrepancies, resolved by consensus.

Limitations

One of the limitations in this systematic review is the heavy reliance on one institution (Massachusetts General Hospital) 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 5). 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 overall survival rates reported in both proton and photon studies were comparable to those reported in the literature such as COG A9961 Phase III 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 proton therapy have no differences in disease control outcomes compared with photon-treated patients.

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 take into account the competing risks of death using more rigorous methodology (i.e. 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 one or two 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, TIAs, aneurysm) and cardiovascular disease (48,49). 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 TIAs tend to develop 20-25 years after CSI, whereas aneurysms can develop over 30 years after treatment (49,50). Cardiovascular disease is also difficult to study as the risk of cardiac mortality increases substantially after 25-30 years (51), 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 which take into account the competing risks of treatment failure and death. Additionally, we restricted our analysis to patients with medulloblastoma 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 proton beam therapy. 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.

Conclusions

In this systematic review, we show that there is moderate grade clinical evidence supporting proton therapy as the preferred delivery technique for both children and adults with medulloblastoma requiring craniospinal radiotherapy, largely on the basis of superior intellectual outcomes, decreased hypothyroidism, and improved acute toxicity 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.

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Figure 1: PRISMA flowchart

Table 1: PICO selection criteria
Table 2: Overview of study endpoints reported
Table 3: Overview of included studies on proton beam therapy for medulloblastoma patients

Table 1. PICO selection criteria

Selection Criteria	Inclusion criteria	Exclusion criteria
Population	Both adults and children with medulloblastoma	
Intervention	Proton beam therapy for CSI	Photon therapy only, carbon ion therapy, studies in which craniospinal irradiation or tumour boost were not described (i.e. 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-modelling
Study designs	Case series of >5 medulloblastoma patients, 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 or congress abstracts
Language	English	All other languages

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	Hypothy-roidism	Other endocrin-opathies	Oto-toxicity	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														

Kuhlthau 2012	4	142	Unclear									■					
Tran 2020	5	15	51 months median	■						■		■					
Kralik 2017	5	25	4.3 years median										■				
Vogel 2019	5	39	19.6 months median										■				
MacEwan 2017	5	6	13.6 years median											■			
Min 2014	4	12	1.25 years median												■		
Jimenez 2013	4	9	39 months median	■					■	■							
Ray 2013	4	9	14 months median	■													
Grieco 2020	6	31	3 years mean				■										
Pulsifer 2015	4	23	2.5 years mean				■										
Pulsifer 2018	5	52	3.6 years mean				■										
Trybula 2021	7	79	4.75 years mean														■

Legend:

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 compared to photons

Table 3. Overview of included studies on proton beam therapy for medulloblastoma patients

*Note that studies are reported only once in this table, and grouped with their primary reported endpoint. Several studies report in more than 1 outcome category.
** Please see Supplementary 4 for detailed information of how NOS scores for each study were assigned.
● indicates "high-quality" studies (comparative study; NOS score ≥6) that were most influential in forming the conclusions of the systematic review

Study / NOS score	Method	Patient characteristics	Follow Up	Treatment Details	Control group	Select reported outcomes	Statistical methods for incidence rate	Comments
Disease control (N= 5)								
Paulino et al. 2021; Houston, USA NOS**: 8/9 ●	Retrospective; comparative by timeframe; enrollment between 1996-2014	- 115 MB patients, including 52 patients treated with PT and 63 patients treated with photon therapy - Median age was 7.0 years in both groups (range: 3-17 years) - 73/115 patients had standard-risk MB	Median FU (PT): 8.7 years (0.4-13.4 yr) Median FU (Photon): 12.8 years (0.2-20.3 yr)	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-year) was similar for the PT and photon cohorts (80.3% and 80%, respectively) - OS (10-year) was similar for PT and photon cohorts (72.4% and 78.1%, respectively) - For standard-risk MB patients only, 5-year OS and 10-year OS was 84.5% and 84.5%, respectively for photon cohort and 93.8% and 85.3%, respectively, for the PT cohort (p = 0.55) - For high-risk MB patients, the 5-year OS and 10-year OS was 68.5% and 63.2%, respectively, for photon cohort and 56.1% and 49.9%, respectively, for PT cohort (p = 0.40) - 10-year secondary malignancy incidence was 8% for the photon and 4.9% for the PT cohort (p = 0.74) - There was no difference in the distribution of patients according to sex, age at radiotherapy (07 or >7 years), risk category, CSI dose (18.0- 23.4 vs 30.6-39.6 Gy), or type of chemotherapy - Median patient age at time of radiotherapy was 7.1 years for group I and 7.0 years for group II.	Actuarial rate using Kaplan-Meier method	Robust study. Photon and proton cohort drawn from different time-frames at the same institution. Follow up shorter for PT (8.7 yr) vs photon (12.8 yr) 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[12]; Boston/Atlanta, USA NOS: 9/9 ●	Retrospective; comparative from 2 institutions; enrollment between 2000 to 2009	- 88 all standard risk MB patients, including 45 patients treated with PT and 43 patients treated with photon therapy - Median age was 6.2 years (range: 3-21 years) in the PT cohort - Median age was 8.3 years (range: 3.4-19.5 years) in the photon cohort	Median FU 6.2 years (PT) (95% CI: 5.1-6.6 yrs) 7.0 years (photon) (95% CI: 5.8-8.9 yrs)	Maximal safe resection; all received chemotherapy (variable protocols); passive scatter 3DCPT	43 patients who had photon RT (different institution within the same time-frame)	- OS (6-year) 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-year) 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 time-frame, cohort characteristics were reasonably similar though median age was 2 years older in photon group. Median FU similar btw cohorts: 6.2 years (proton) vs 7.0 years (photon). Molecular subtyping data not reported (likely not available at that time).
Baliga et al. 2021; Boston, USA NOS: 6/9 ●	Mixed (mostly prospective); enrollment between 2002-2016	- 178 MB patients - 102 (57%) standard risk, 16 (9%) intermediate risk; 60 (34%) high risk MB patients - Median age was 8.1 years (2.5 - 24.1 yr)	Median FU 9.3 years (0.5-17.2 years)	Variable extent of surgery, 159 (89%) underwent GTR, variable chemotherapy protocols; passive scatter + PBS PT	No	- OS (10-year) was 79.3% (95% CI: 73.1-85.9%) for the entire cohort - OS (10-year) standard risk was 86.9% (95% CI: 79.9-94.4) - OS (10-year) IR/HR was 68.9% (95% CI: 58.7-80.8) - 10-year cumulative incidence of brainstem injury 1.9% (95% CI: 0.5-5.1) - 10-year cumulative incidence of secondary malignancy 2.1% (95% CI: 0.6-5.8) - Median time to progression 1.6 year (0.22-10.3) - EFS (10-year) standard risk was 79.5%	Actuarial rate: Cox & Fine-Gray model for competing risks	Longest follow up reported on the MGH proton cohort (median 9.3 years). No comparative photon group. Molecular subtyping data not reported (likely not available at that time).

Jimenez et al. 2013; Boston, USA NOS: 4/9 Individual patient data re-analyzed	Retrospective; cohort; enrollment between 2002-2010	- Cohort of 15 very young MB/SPNET patients, including 12 MB patients - 9 MB patients underwent CSI (included in our analysis) - Median age 37 months (23-55 months)	Median FU 39 months (3-102 months)	Maximal safe resection; all received chemotherapy (variable protocols); passive scatter 3DCPT	No	- Hearing loss in 7/9 (77.8%) patients - Grade 2 endocrinopathy in 2/9 (22.2%) patients - LF (3-year): 0/9 (0%) patients - OS (3-year): 9/9 (100%) patients	Actuarial rate by Kaplan Meier	Small cohort of very young SPNET/MB patients 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 re-analysis. FU duration insufficient for OS or endocrinopathy.
Ray et al. 2013; Indianapolis, USA NOS: 4/9 Individual patient data re-analyzed	Retrospective; cohort; enrollment between 2004-2012	- 22 pediatric patients with leptomeningeal spinal mets - 9 MB patients - Mean age 5.7 years (range: 2-11 years)	Median FU was 14 months (4 to 33 months)	No details	No	- Local Control (12 months) was 68% for entire cohort - OS: 7/9 (77.8%) for MB patients	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 MB patients fit study criteria. Data re-analyzed. However, FU insufficient to draw conclusions about OS or local control.
Patterns of Failure (N= 1)								
Sethi et al. 2014; Boston, USA NOS: 5/9	Retrospective; cohort; enrollment between 2002-2011	- 109 MB patients - Median age was 7.4 years (range: 2.2-22.7 years) - 74 (68%) standard risk, and 35 (32%) high risk MB patients	Median FU was 38.8 months (range: 1.4-119.2 months)	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) - Linear energy transfer (LET) distribution calculated by Monte Carlo, no correlation between recurrence and low LET - Local failure was 16/109 (15%) - Overall survival was 97/109 (89%) - Median time to recurrence was 18.6 months (range: 2.8-38.9 months)	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.
IQ (N = 5)								
Eaton et al. 2021; Boston, USA NOS: 8/9 o	Prospective; cohort; comparative from 2 institutions; enrollment between 2000-2009	- 37 MB patients with neurocognitive data (17 patients treated with PT; 20 patients treated with photon radiation) - Median age of PT cohort: 7.3 years (range: 3.4-20 years) - Median age of photon cohort: 8.1 years (range: 4.5-16.6 years) - All standard risk MB patients	Median FU in PT cohort: 5.3 years (range: 1-11.4 years) Median FU in photon cohort: 4.6 years (range: 1.1 ï 11.2 years)	All patients underwent maximal safe resection of the primary tumour and chemotherapy; 3DCPRT	50 patients§ propensity score matched 1:1 PT cohort of 25 obtained from MGH; photon cohort of 25 obtained from Emory University; same time frame	- Patients treated with PT radiation performed higher in IQ scores (p = 0.021), verbal comprehension (p = 0.01) and perceptual reasoning (p = 0.011) at FU compared with patients treated with photon radiation - PT cohort was comparable to the photon cohort in relation to processing speed (p = 0.331) and working memory (p = 0.388) - Photon cohort had higher degree of variation in outcomes i.e. 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 yr median FU for proton-treated patients (longest follow-up). 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, follow-up time) were similar. *Baseline neurocognitive measurements were only taken for the proton cohort, not the photon cohort.
Kahalley et al 2020; Toronto, Canada / Houston, USA NOS: 9/9 o	Retrospective; comparative; enrollment between 2007-2018	- 79 MB patients - 37 patients treated with PT, 42 patients treated with photon therapy - Mean age at diagnosis was 8.9 years (3.5-14.4 years) for patients treated with PT - Mean age at diagnosis was 8.4 years (3.6-15.3 years) for patients treated with photon therapy - 57/79 patients had standard risk-MB	Mean FU within the PT cohort: 3.7 years (range: 0.1-10.9 years) Mean FU within the photon cohort: 4.8 years (range: 0.9-9 years)	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 time frame	- Patients treated with PT exhibited stable intellectual outcomes in most domains and had significantly better long-term global IQ (p=0.009), perceptual reasoning (p=0.022) and working memory scores (p=0.002) after 4 years compared to 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=0.003)	Use of descriptive statistics with different IQ/cognitive scales. N/A no actuarial methods	Multi-institutional matched cohort study with median FU 3.7 years for proton cohort. Proton cohort drawn from Texas Children's Hospital, photon cohort drawn from The Hospital for Sick Children (Canada) in same time-frame. Clinical and demographic variables were not significantly different from each other. Cohorts were matched by risk type, age, sex, maternal education, paternal education. *Baseline scores were missing for 15 XRT and 4 PRT pts.

Pulsifer et al. 2015; Boston, USA NOS: 4/9	Retrospective; enrollment between 2002-2013	- 23 MB patients out of the total sample (N = 60) - Mean age of all patients: 12.3 years (range: 6.3-21.7 years)	Mean FU: 2.5 years for all patients (range: 1-8.3 years)	12 patients received a biopsy; 20 patients received near/STR; 26 patients received GTR; 37 patients received chemotherapy; patients treated with passive scatter 3DCRT	None	- No significant change in IQ, verbal comprehension, perceptual reasoning, or working memory at FU - Processing speed declined significantly (p = 0.003) in patients who received CSI, with a greater decline in younger (<12 years) 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 proton therapy from MGH; mixed diagnoses, only 23/60 were MB patients treated with CSI. Demographic and treatment information available for patients treated with CSI. Small sample size, short median FU of 2.5 years.
Pulsifer et al. 2018; Boston, USA NOS: 5/9	Prospective; cohort; enrollment between 2002-2017	- 52 MB patients out of total sample (N =155) - Mean age of all patients: 8.9 years (range: 1-22.5 years)	Mean FU: 3.6 years (range: 1.1-11.4 years) for all patients	18 patients received biopsy, 54 patients received near/STR, 79 patients received GTR; 98 patients received chemotherapy; patients received passively scattered 3DCRT	None	- Overall, mean IQ declined slightly at FU for the entire cohort - Significant IQ decline in patients less than 6 years old who were receiving CSI - Adaptive functioning score declined in patients that received CSI and were less than 6 years old, but improved in older patients (> 6 years) - 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 same author as above with median FU 3.6 yrs. Also a cohort with mixed diagnoses; 55/155 were MB patients treated with CSI. IQ and demographic data was not available separately for medulloblastoma subgroup, therefore conclusions cannot be drawn regarding our research question. Only 73% of pts followed up with for cognitive functioning. IQ, but 147/155 pts followed up with for adaptive functioning.
Grieco et al. 2020; Boston, USA NOS: 6/9	Retrospective; nested case control; no enrollment dates provided	- 58 patients with PF tumor included in the study - 31 MB patients eligible for the study - Mean age 7 years (range: 1.2-15.8 years)	Mean FU: 3 years (SD = 2.24)	Median of 35 day interval between surgery and PT radiation; 29 patients underwent GTR, 7 patients underwent STR; 31 patients had chemotherapy; patients treated with passive scatter 3DCRT	All patients received proton radiation therapy; 18 patients who had cerebellar mutism syndrome (16/18 MB) were matched with 18 non-CMS pts (15/18 MB)	- 18 (31%) patients developed post-op pediatric cerebellar mutism syndrome - Longitudinal neuropsychological outcomes for post-operative pediatric CMS patients who underwent PT did not differ significantly from those without CMS who underwent PT - At 3 years, overall intelligence, receptive/expressive vocabulary, behavioural inhibition, emotional control, mood, anxiety was 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 proton-treated patients with post-op pediatric cerebellar mutism syndrome 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; Boston, USA NOS: 9/9	Retrospective; comparative; enrollment between 2000-2009	- 77 MB patients including 40 patients treated with PT and 37 patients treated with photon therapy - Median age for patients treated with PT: 6.2 years (range: 3.3-21.9 years) - Median age for patients treated with photon therapy: 8.3 years (range: 3.4 – 19..5 years) - All patients had standard risk MB	Median FU for patients treated with PT: 5.8 years (range: 3.4-9.9 years); Median FU for patients treated with photon therapy: 7 years (3.5 - 13.5 years)	Maximal safe resection; chemotherapy protocol of vincristine, cisplatin, cyclophosphamide, and/or lomustine; passively scattered 3DCRT PT	37 MB patients treated by photon CSI. Patients in the proton cohort came from MGH, while patients in the photon cohort came from Emory University; time frame was the same for both cohorts	- PT was associated with reduced risk of hypothyroidism compared to photon cohort (23% vs 69%, p = 0.001), sex hormone deficiency (3% vs 19%; p = 0.025), and requirement for endocrine replacement therapy (55% vs 78%; p = 0.03) - Greater height standard deviation score in the PT cohort vs photon cohort (Mean ± SD: -1.19 ± 1.22 vs -2 ± 1.35; p = 0.02) - No significant difference in incidence of growth hormone deficiency (53% vs 57%, p = 0.708), adrenal insufficiency (5% vs 8%, p = 0.667), or precocious puberty (18% vs 16%, p = 0.881)	Crude rate; only survivors analyzed, therefore no competing risk required	PRT cohort was significantly younger than XRT cohort, but cohorts were similar in other respects (i.e. gender, risk-type). Median FU was slightly longer for XRT vs PRT cohort (7 vs 5.8 yr), but FU duration 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).
Aldrich et al. 2021; Houston, USA NOS: 6/9	Retrospective; comparative; enrollment between 1997-2016	- 118 MB patients including 64 patients treated with PT and 54 patients treated with photon therapy - Mean age of patients treated with PT: 6.83 years (SD: 3.2) - Mean age of patients treated with photon therapy: 8.47 years (SD: 4.04) - Age range of total sample (2-18 years) - 77 patients had average risk MB and 41 patients had high risk MB	Median FU for all patients: 5.6 years (range: 1 – 10 years)	Maximal resection in all patients; multi-agent chemotherapy; passively scattered PT	54 patients treated with photon CSI at Texas Childrenś 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. study)	- The PT cohort had a significantly lower incidence of primary hypothyroidism compared to photon cohort (6% vs 28%; HR = 4.61; 95% CI: 1.2 – 17.66, p = 0.03) - 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=0.01)	Actuarial rate estimated with KP	Not explicitly stated, but patient population likely overlaps significantly with Bielamowicz et al. Median FU 5.6 years 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 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 prior to radiotherapy

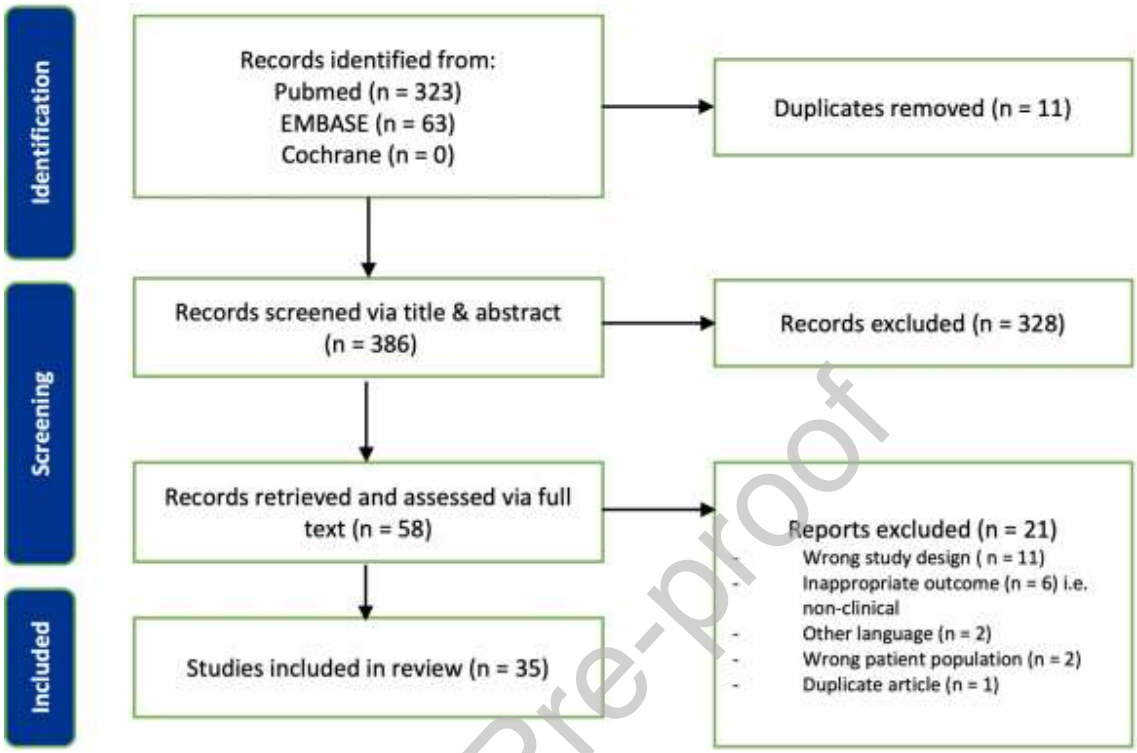
Bielamowicz et al. 2018; Houston, USA NOS: 7/9	Retrospective; comparative; enrollment between 1997-2014	- 95 MB patients, including 41 patients within a PT cohort, and 54 patients within a photon therapy cohort - Median age for patients treated with PT: 7 years (range: 2.3-14.4 years) - Median age for patients treated with photon therapy: 8.2 years (range: 2-18 years) - 25 standard risk MB patients and 15 high risk MB patients within the PT cohort - 41 standard risk and 13 high risk MB patients within the photon cohort	Median FU for patients treated with PT: 3.8 years (range: 1 ï 8.8 years) Median FU for patients treated with photon therapy: 9.6 years (range: 1 ï 15.8 years)	Maximal resection in all patients; all patients treated with chemotherapy, variable protocols; passively scattered PT	54 patients treated with photon CSI. All patient medical records came from Texas Childrenös 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 = 0.14) - Primary hypothyroidism was numerically, but not significantly, lower in PT cohort compared to photon cohort (15.8% vs 22.2%; HR = 2.1, p = 0.27) - Central hypothyroidism was numerically, but not significantly, lower in PT cohort compared to photon cohort (18% vs 24%; HR = 2.16, p = 0.18)	Crude rate 84/95 patients alive at time of analysis.	Significantly longer median follow-ups for photon-treated patients compared to protons (9.6 vs 3.8 yr). Patients all had pre-radiation thyroid function labs. Cohorts are similar in age, gender, and risk type. No other characteristics described.
Vatner et al. 2018; Boston, USA NOS: 5/9	Prospective; enrollment in 3 prospective studies from 2003-2016	- 222 patients with brain tumours - 130 eligible MB with CSI - Median age of all patients: 7.4 years (range: 1.1 ï 25.9 years)	Median FU: 4.4 years (range: 0.1 ï 13.3 years)	All MB pts resected and underwent chemotherapy (variable protocols); passively scattered 3DCRT PT	No	- 5-year 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 MB patients had endocrinopathies prior to 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; Houston, USA NOS: 8/9	Retrospective; enrollment between 1997-2013	- 84 MB patients, including 38 patients treated with PT and 46 patients treated with photon therapy - Median age for the PT cohort: 7.6 years (range: 2.9-14.5 yeras) - Median age for the photon therapy cohort: 9 years (range: 3-18 years) - 24 standard risk and 14 high risk MB patients within the PT cohort - 34 standard risk and 12 high risk MB patients for the photon cohort	Median FU in the PT cohort: 56 months (range: 17 ï 101 months); Median FU in the photon therapy cohort: 66 months (range: 13-163 months)	Maximal safe resection in all; cisplatin-based chemotherapy delivered 4 weeks after RT; amifostine was provided for all PT patients, and 19 (41%) photon patients; passively scattered PT	46 patients treated with photon IMRT within the same time frame 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 months adequate for ototoxicity outcome. Mean cochlear dose and mean cisplatin dose was reported. Audiograms scheduled before and after RT.
Yock et al. 2016; Boston, USA NOS: 6/9	Prospective single arm phase 2 trial; enrollment between 2003-2009	- 59 MB patients - Median age: 6.6 years (3-21 years) - 39 Standard risk, 6 intermediate risk and 14 high risk MB patients	Median FU: 5.2 years (IQR: 5.2-8.6 years)	Maximal safe resection; all patients treated with chemotherapy, variable protocols; passively scattered PT	No	- Cumulative incidence of grade 3-4 hearing loss was 12% at 3 years (95% CI: 4-25) and 16% at 5 years (95% CI: 6-29) according to Pediatric Oncology Group ototoxicity scale - Hearing at 5-year FU was the same/improved compared to baseline in 35% of ears and worsened in 65% of ears - 3-year PFS was 83% (95% CI: 71-90); 5-year PFS and OS was 80% (95% CI: 67-88) and 83% (95% CI: 70-90), respectively - Cumulative incidence of any neuroendocrine deficit at 7-year FU was 63% (95% CI: 48-75) - 7-year 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 < 0.0001)	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 5.2 years adequate for most outcomes.

Moeller et al. 2011; Houston, USA NOS: 5/9	Prospective; enrollment between 2006-2009	- 19 MB patients - Mean age: 6 years (range: 3-16 years) - 16 Standard risk and 3 high risk MB patients	Mean FU: 11 months (range: 8 t 16 months)	All patients received platinum-based chemotherapy; no surgical details; passively scattered PT	No	- Hearing sensitivity declined post-radiation for all frequencies tested (0-9 kHz, p < 0.05) - 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 post-therapy	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; Houston, USA NOS: 8/9	Retrospective; comparative; enrollment between 2003-2011	- 40 MB patients treated with vertebral body sparing CSI - 19 MB patients treated with PRT radiation; 21 MB patients treated with photon radiation - Median age within the PT cohort was 29.9 years (range: 16.9-49.9 years) - Median age for the photon cohort was 32.7 years (range: 16.6-60.4 years - 14 average risk MB patients and 5 high risk MB patients in the PT cohort - 14 average risk and 5 high risk MB patients in the photon cohort	Median FU in PT cohort: 2.19 years; median FU in photon cohort: 4.76 years	All patients underwent surgical resection of primary tumour; 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 = 0.004) and had fewer patients with >5% weight loss (16% vs 64%, p = 0.004) - PT cohort experienced less gr. 2 nausea and vomiting photon cohort (26% vs 71%, p = 0.004) - PT cohort had less myelosuppression: reduction in peripheral WBC, Hb, and platelets compared to photon cohort (p 00.05) - Similar results seen after excluding patients who received chemotherapy pre-CSI - 2-year 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<0.001)	Crude rate	Comparative study of adult patients treated with PT vs photons from MD Anderson. Follow-up of 2.2 yr for protons sufficient for assessment of acute toxicities.
K Liu et al. 2021; Boston, USA NOS: 8/9	Retrospective; comparative; multi-institutional; enrollment between 2000-2017	- 97 MB patients; 60 MB patients treated with PT radiation; 37 MB patients treated with photon - Median age within the PT cohort was 7.5 years (range: 3.5-22.2 years) - Median age within the photon cohort was 9.9 years (range: 3.6-19.5 years) - 52 (87%) standard risk MB patients and 8 (13%) high risk MB patients within the PT cohort - 33 (89%) standard risk and 4 (11%) high risk within the photon cohort	Median FU in PT cohort was 8.1 years (range: 0.2-13.7 years) Median FU in the photon cohort was 7.1 years (range: 0.2-17.5 years)	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 proton therapy; vertebral-body-sparing for patients aged >15 years	37 patients treated with photon RT in the same time frame 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 = 0.044), lymphopenia (p < 0.0001), anemia (p = 0.011), thrombocytopenia (p = 0.066) in the photon cohort compared to the PT cohort - No difference in WBC counts, neutrophil counts, or hemoglobin concentration between cohorts - 5-year OS rates not statistically different between the PT and photon cohort (89.6% vs 93.4%, p = 0.2129) - 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 to the photon cohort - Platelet counts and lymphocyte counts were significantly higher in the PT cohort compared to the photon cohort during treatment period	Crude rate. No discussion of competing risk of death	Comparative study of acute toxicities in typical medulloblastoma demographic (children). Long FU duration. No significant difference in age, sex, MB risk type between cohorts.
Song et al. 2014; Seoul, Korea NOS: 8/9	Prospective; cohort; enrollment between 2008-2012	- 43 patients with pediatric CNS tumors (13 eligible MB patients) - Median age of the total sample was 10 years (2-18 years)	Median FU was 22 months (2-118 months)	No surgery details; 84% received chemotherapy; passive scatter	13 pts treated with photon RT between 2003-2012 at the same institution (retrospective)	- Incidence and severity of thrombocytopenia was less severe in PT group compared to photon (p=0.012) - Leukocyte and platelet recovery rate significantly greater in PT cohort compared to photon (p=0.003; p=0.010) - Diarrhea reported by 23% vs 0% in photon vs PT group (p=0.023)	Unclear, likely crude rate	Prospective PT cohort of compared with retrospective photon cohort from same institution. Both cohorts had baseline assessment prior to treatment. Median FU 22 months sufficient for outcome of interest. Rare study from Korea.
Hashimoto et al. 2019; Sapporo, Japan NOS: 5/9	Retrospective; comparative; enrollment between 2016-2018	- 17 patients with MB and germ-cell tumours were treated with CSI - 6 MB patients within the PT cohort; 1 MB patient within the photon cohort - Median age was 11 years (range: 7-19 years)	Mean FU: 4 weeks	No details about surgery provided; variable chemotherapy; vertebral-body-sparing IMPT CSI technique with spot scanning	8 patients treated with photons (1 MB patient within this cohort) at same institution and time	- Both nadir WBC, Hgb, and platelet levels and levels 4-weeks after CSI were higher in PT than photon group (p<0.05), suggesting less myelosuppression for PT - Adolescent and young adults (>15yo) experienced lower incidence of serious acute hematological toxicity when treated with PT compared to photon CSI	Crude rate. No discussion of competing risks	Median FU 4 weeks short, but may be sufficient for measurement of acute toxicities. WBC, Hb and platelets were measured at the start and at 4 weeks post-CSI. Very small sample size.

		- 5 average risk MB patients and 2 high risk MB patients within the sample						
I Liu et al. 2021; Jacksonville, Florida NOS: 4/9	Retrospective; cohort; enrollment between 2008-2020	- 20 adult MB patients - Median age 27 (range: 22-30 years) - 11 standard risk and 9 high risk MB patients	Median FU 3.1 years (0.6ï12.7 years)	Variable (including surgery and chemotherapy); passive scatter + PBS	No	- No Ô grade 3 acute hematologic toxicities due to CSI - 5/14 (36%) patients had grade 2 leukopenia - Most common grade 2 acute toxicities: anorexia, nausea - OS 95% (95% CI 72ï99) - 4-year local control 90% (95% CI 53ï99)	Actuarial rate calculated	Small cohort of adult MB. Only 14 pts were included in hemotaological toxicity analysis (baseline CBCs taken). FU duration inadequate for OS but sufficient for acute toxicity.
Suneja et al. 2013; Philadelphia, USA NOS: 3/9	Retrospective; enrollment between 2010-2012	- 48 patients in total (9 MB/PNET patients) - Median age for all patients was 10.8 years (range: 1-22 years)	No FU after completion of RT	Only 8 of 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 out of 48 patients had Lanksy performance recorded (all patients appear to be accounted for for other acute toxicities)
Health-related QoL (N = 4)								
Eaton et al. 2020; Atlanta, USA NOS: 5/9	Mixed; combined patients from 2 prospective trials and a retrospective review with additional patients; enrollment between 2004-2011; multi-institutional	- Cohort of 40 very young patients (<4 years) - 5 eligible MB patients treated with CSI - Median age for total sample was 2.5 years (range: 3.1-3.9 years)	Median FU: 6.7 years (range: 3-15.4 years)	All patients received chemotherapy; surgery details not specified; radiotherapy technique not specified	No control group, but HRQoL scores compared with published cohorts of healthy children (n=401) and chronically ill pts (n=367)	- According to both parent and child reports, patients had significantly lower psychosocial, emotional, social and school-related quality of life scores compared to published healthy children cohort - Greater than 1/3 of parent reported HRQoL scores were within a previously defined range for healthy children - QoL scores were not significantly different compared to the published cohort of patients with benign chronic health conditions for any of the QoL categories - There was no statistically significant association between HRQOL and whether CSI vs IFRT was given - 90% of children functioned in a regular classroom, 14 (36%) used a classroom aid, 18 (46%) had an individualized education plan	Crude rate. No discussion of competing risks	Cohort of very young MB patients (median age 2.5 yr). 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 afterwards. Median FU 6.7 yrs adequate for outcome of interest. Outcomes were self-reported and parent-reported.
Kamran et al. 2018; Boston, USA NOS: 6/9	Prospective; enrollment between 2002-2015	- 116 MB/PNET patients (108 MB pts) included in the study - 50 MB/PNET patients were derived from the Kuhlthau et al. 2012 study - Median age of all patients: 7.6 years (range: 2-18 years) - Risk ï 77 standard risk and 39 high risk patients	Median FU: 5 years (range: 1 ï 10.6 years)	Proton radiation technique, chemotherapy and surgery not detailed in the study	No control group; findings compared with previously published cohorts of healthy children	- QoL was determined through child reports and parent proxy reports according to the PedsQL criteria - Total Core score ($p < 0.001$), physical score ($p < 0.001$), and psychosocial scores ($p = 0.006$) were low at the time of diagnosis, but improved significantly over time for all patients - Total core score, physical score, psychosocial score, and school QoL metrics were significantly worse than healthy children ($p < 0.001$ for all metrics) according to parent proxy reports - Longer follow ups were associated with greater improvements in HRQoL - Only physical score ($p = 0.024$) was significantly worse than a published cohort of healthy children, according to child report - Socioeconomic status did not appear to impact HRQoL	Crude rate. No discussion of competing risks	Cohort of typical range of MB patients. Included both self-reported and parent reported QoL (although parent-reported QOL missing for some patients). Patients assessed once during first 2 weeks of RT, once during last 2 weeks, and annually thereafter. Mean follow up duration was ~5 years, but not all patients accounted for in follow up. Contained 50 MB pts from the Kuhlthau study (longer follow up in this study).
Kuhlthau et al. 2012; Boston, USA NOS: 4/9	Prospective; enrollment between 2004-2010	- 142 MB/PNET patients - Mean age of all patients: 8.5 years (no range provided)	Average FU interval is unclear	119 patients received definitive surgery; 88 patients received chemotherapy; proton radiation technique was not specified	No	- HRQoL increased significantly over time in patients who received CSI ($p = 0.0202$) according to PedsQL total core score metric	Crude rate. No discussion of competing risks	Included both self reported and parent reported QoL, follow-up duration too short (3 years) and *only 43 out of 142 patients available for 3-year follow up). **Large proportion of patients not accounted for during baseline measurements (106/142)
Tran et al. 2020; Geneva, Switzerland NOS: 5/9	Retrospective; cohort; enrollment between 1997-2017	- 221 pediatric patients with CNS tumors - 15 MB patients - No details on age and disease characteristics or number of patients receiving CSI	Median FU was 61 months (range: 4-222 months)	No details on surgery/ chemotherapy; no details on CSI; pencil beam PT	No	- Cognition/Social function scores worsened over time - Family function/Global well-being scores improved over time after treatment - 1/15 MB patients developed grade 3 hearing impairment - OS (5-year) was 64% (95% CI: 38.4-89.6) for MB patients - 5-year disease control was 50% (95% CI: 23.1-76.9) for MB patients	Actuarial rate used for disease control by Kaplan Meier. Crude rate for QoL	Multiple diagnoses; data reported for MB subgroup but no individual patient-level data was available (unclear how many received CSI). Quality of life was assessed (self-reported), but primary outcome was overall survival. Median FU for entire cohort was 4.12 years.
Brainstem Injury (N = 3)								

Gentile et al. 2018; Boston, USA NOS: 6/9 o	Retrospective; enrollment between 2000-2015	- 216 patients, including 151 eligible MB patients treated with CSI - Median age of all patients: 6.6 year (range: 0.5-23.1 year)	Median FU of all patients: 4.2 years (range: 0.1-15.3 years)	All patients underwent surgery to various extents; 180 (83.3%) patients treated with chemotherapy; passively scattered PT	No	- 5-year cumulative incidence of brainstem injury was 2.0% (95% confidence interval, 0.7%-4.8%) for all patients - Crude rate of injury was 1.9% (3) for MB patients - Clinical manifestations of brainstem injury in 3 MB patients, including ataxia, right-side weakness, quadriplegia, and ventilator dependence - 3 and 5-year overall survival for total sample was 95% and 87.3% respectively	Actuarial rate: death defined as competing risk	Multiple diagnoses, 151/216 patients were MB treated with CSI. Individual study data available for patients with brainstem injury, able to re-analyze data for MB population. Median follow-up of 4.2 years for 198 surviving patients (> 90% of cohort), sufficient for outcome of interest.
Giantsoudi et al. 2016; Boston, USA NOS: 6/9 o	Mixed; 84 patients enrolled in a prospective trial with remainder of patients studied retrospectively; enrollment between 2002-2011	- 111 MB patients - Median age: 7 years (range: 32 months-22 years) - 76 standard risk and 35 high risk MB patients	Median FU: 4.2 years	Details of surgery not specified; only 4 patients specified to have received chemotherapy; passively scattered PT (avoiding brainstem doses >54Gy)	No	- 5-year cumulative incidence of symptomatic CNS radiation injury was 4/111 (3.6%), with 3/111 (2.7%) having a grade 3+ injury - 5-year cumulative incidence of brainstem 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. RBE values were estimated based on LET-based published models.
Vogel et al. 2019; Philadelphia, USA NOS: 5/9	Prospective; registry; enrollment between 2012-2018	- 166 patients, including 39 MB patients - Median age of all patients: 10 years (range: 0.5-21 years)	Median FU: 19.6 months (range: 2-63 months)	160 patients resected; pencil beam PT	No	- Actuarial incidence of brainstem necrosis was 1/166 (0.7%) at 24 months (95% CI: 0.1-5.1%) - The only patient who developed brainstem toxicity was a 12-yo MB patient who had been previously treated with twice-daily photon RT (brainstem Dmax 61.2Gy) and intrathecal methotrexate at a different institution	Actuarial rate by Kaplan Meier	Prospective registry cohort of multiple diagnoses, small number of MB patients (39/166). Median follow-up of 19.6 months is insufficient for outcome of interest.
Radiation-induced large vessel cerebral vasculopathy (N = 1)								
Kralik et al. 2017; Indianapolis, USA NOS: 5/9	Retrospective; enrollment between 2007-2014; endpoint: Radiation-induced large vessel cerebral vasculopathy (RLVCLV)	- 75 patients, including 25 MB/PNET patients - Mean age of all patients: 7.9 years (range: 1.5 ï 18 years)	Median FU for all patients: 4.3 years (range: 0.6 ï 9.6 years)	Details of surgery, chemotherapy, and PT technique are not specified	No	- Radiation-induced large vessel cerebral vasculopathy (RLVCLV) present in 1 (4%) MB patient, who presented with an acute pontine infarct located in the cerebellum - Time to RLVCV development in the MB patient was 7.5 years	Actuarial rate by Kaplan Meier	Multiple diagnoses, 25/75 patients were MB. Individual patient data available for those who developed RLVCLV, data re-analyzed based on this. Individual patient demographic data or subgroup demographic data not available.
Scoliosis/ (N = 1)								
MacEwan et al. 2017; Loma Linda, USA NOS: 5/9	Retrospective; case series; enrollment between 2001-2007	- 6 very young MB patients - Median age at radiotherapy was 3.8 years (range: 3.1-5.1 years) - All patients had high risk MB	Median FU was 13.6 years (range: 8.7-15.8 years)	Maximal safe resection; all patients treated with chemotherapy; PT technique not specified (patients not treated with RT until 3+ yrs old)	No	- 2 (40%) patients had scoliosis at follow-up, 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 follow-up - 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 PRBC transfusion - 1/6 patients experienced esophagitis - Disease-free survival and overall survival were 83% at FU - All patientsö heights were below the 10th-percentile, and all were initiated on GH replacement therapy	No statistical analysis performed	Very small sample size, all patients were high risk MB. Median FU 13.6 yrs adequate. One patient died prior to clinical/radiographic follow up.
Radiation-induced cavernoma (N = 1)								
Trybula et al. 2021; Chicago, USA NOS: 7/9 o	Retrospective; cohort; enrollment between 2003-2019; endpoint: RT-induced cavernous malformation	- 79 MB patients, including 49 patients treated with PT and 30 patients treated with photon therapy - Mean age was 9.6 years for the PT cohort and 8.8 years for the photon therapy cohort (total sample range: 3.2-18.3 years)	Mean FU for the PT cohort was 56.8 months and 105 months for the photon therapy cohort	All patients surgically resected for primary tumour; all patients treated with chemotherapy; PT technique not specified	30 patients treated with photon RT in the same time frame at the same institution	- 26 (86.7%) patients treated with photon RT and 42 (85.7%) patients treated with PT developed post-radiation CMs. - Average time to CM development was shorter in the proton cohort compared with the photon cohort (18.2 months vs 40.2 months, p = 1.98e-4)	Actuarial rate by Kaplan Meier	Similar demographics (age, treatment) between proton and photon cohort. Baseline pre-treatment MR was done in all patients assess for CM. Median FU 7.2 years sufficient for outcome of interest.
Permanent alopecia (N = 1)								
Min et al. 2014; Boston, USA	Unclear study design and years of enrollment	- 12 MB patients; - Median age was 6 years (range: 4-15	FU was greater than 1.25 years	No surgical details; all patients received either	No	- 9 (75%) patients had permanent alopecia; 7 (58%) patients had Grade 2 permanent alopecia - All high-risk MB patients showed either grade 1 or 2	Crude rate. No discussion of competing	Unclear study design, unclear years of enrollment and small sample size. Duration of FU likely too short for assessment of permanent alopecia.

NOS: 4/9		years) - 5 standard risk and 7 high risk MB patients		conventional dose or high dose chemotherapy; passively scattered PT		- permanent alopecia 2/5 standard-risk MB patients had grade 1 or 2 permanent alopecia	risks	



Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: