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REVIEW

A review of dosimetric and toxicity modeling of proton versus photon craniospinal irradiation for pediatrics medulloblastoma

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ABSTRACT

Background: Craniospinal irradiation (CSI) is the standard radiation therapy treatment for medulloblastoma. Conventional CSI photon therapy (Photon-CSI) delivers significant dose to surrounding normal tissue (NT). Research into pediatric CSI with proton therapy (Proton-CSI) has increased, with the aim of exploiting the potential to reduce NT dose and associated post-treatment complications. This review aims to compare treatment outcomes of pediatric medulloblastoma patients between Proton- and Photon-CSI treatments.

Material and methods: A search and review of studies published between 1990 and 2016 comparing pediatric (2–18 years) medulloblastoma Proton- and Photon-CSI in three aspects – normal organ sparing and target coverage; normal organ dysfunction and second malignancy risks – was completed.

Results: Fifteen studies were selected for review and the results were directly compared. Proton-CSI reported improved out-of-field organ sparing while target coverage improvements were inconsistent. Normal organ dysfunction risks were predicted to be lower following Proton-CSI. Secondary malignancy risks (SMRs) were generally lower with Proton-CSI based on several different risk models.

Conclusions: Proton-CSI conferred better treatment outcomes than Photon-CSI for pediatric medulloblastoma patients. This review serves to compare the current literature in the absence of long-term data from prospective studies.

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Introduction

Medulloblastoma is the most common central nervous system (CNS) cancer amongst pediatric patients with more than 80% of the patients diagnosed with medulloblastoma under the age of 15 years [1]. It is associated with survival rates of 70–85% after post-surgical chemo-radiotherapy treatment [2]. Craniospinal irradiation (CSI) is the standard radiation therapy treatment for medulloblastoma due to high propensity of medulloblastoma to disseminate throughout the neuro-axis.

Given that pediatrics have higher survival rates, longer life expectancy and are more likely to develop radiogenic side effects than adults [3], late effects from radiation are major concerns for medulloblastoma patients. Late toxicities associated with CSI including neurocognitive impairment; ototoxicity; endocrine dysfunction; growth impairment; cardiotoxicity and second malignancies. [4] Traditionally, CSI has been delivered with photon therapy (Photon-CSI). Late effects from this treatment have been shown to relate to reduced functionality and quality of life (QOL) [5]. Consequently, other alternative radiation modalities for medulloblastoma were explored in bid to reduce CSI-related toxicities.

A rapid growing radiation modality is proton-delivered CSI (Proton-CSI). Proton therapy is increasingly studied due to the characteristic dose distribution of the proton beam, also known as Bragg Peak phenomenon. Owing to this phenomenon, a proton beam is able to concentrate high doses to the tumor volume while delivering near-zero doses to non-target organs [6]. As a result, interest in Proton-CSI grew, demonstrated by the gradual shift toward Proton-CSI for pediatrics, from 465 cases in 2010 to 694 cases in 2012, in the USA alone [7].

Proton beams theoretically enable high dose-concentration around the target, tumor control and normal tissue (NT) sparing. However, this might not hold true in reality due to uncertainties in relative biological effectiveness (RBE) of protons; its actual value was found to vary with energy, especially at regions of sharp dose fall-off [8,9]. Additionally, Jones et al. [10] argued that tumor control might be compromised due to RBE differences between proton, brain and spinal cord, and medulloblastoma cells. In comparison to RBE of protons, higher RBE in brain and cord tissues would lead to a greater biologic effect while lower RBE of cancer cells would lead to under dosage. This challenged the conventional thought of improved treatment outcomes following Proton-CSI as increased risks of radiation-induced toxicities and tumor recurrence were speculated [10]. Hence, long-term post-treatment follow up studies are required to evaluate the true advantage of protons amidst RBE differences between tissues. Likewise, the treatment

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Supplemental data for this article can be accessed here.

outcomes from Proton-CSI and Photon-CSI should be evidenced based, to justify its use for medulloblastoma patients.

The overall aim of this review is to provide an evidence-base for the treatment of pediatric medulloblastoma patients by comparing treatment outcomes of pediatric medulloblastoma patients between Proton- and Photon-CSI under the following criteria: NT sparing and target coverage; normal organ dysfunction risks; and second malignancy risks.

Material and methods

Search strategy for identification of studies

To ensure all appropriate studies were included, a systematic approach was used to search and select appropriate publications. A primary literature search was carried out of the following databases; Scopus, PubMed, Embase and Science Direct, from January 1990 to September 2016, using the following search term strategies:

1. (Proton AND Proton Therapy) AND Medullo-blastoma AND (CSI AND Craniospinal Irradiation) AND (Toxicity OR Second Malignancy OR Dose Distribution OR Organ Sparing).
2. (Photon AND Photon Therapy) AND Medullo-blastoma AND (CSI AND Craniospinal Irradiation) AND (Toxicity OR Second Malignancy OR Dose Distribution OR Organ Sparing).

Studies published after 1990 were included, as they provided valuable long-term Photon-CSI data toxicity data.

All initially identified articles were assessed (title and abstract ± full text) for relevance based on the inclusion and exclusion criteria (Table 1) and to identify duplicated studies. A secondary manual search was carried out on the reference lists of all included studies to identify any additional relevant literature. Data extraction and evaluation were conducted on all eligible studies. Identified studies were evaluated for level of evidence and quality grading using Downs and Black checklist, articles with scores between 0 and 7 were rated as 'Poor', 8–14 as 'Fair', 15–21 as 'Good' and 22–28 as 'Excellent' [11].

Statistical analysis

Plan comparisons of dose distribution between Proton- and Photon-CSI were based on target conformity and homogeneity with the respective indices. Dose-volume histogram (DVH) of the target and NTs were reviewed for evaluation of NT sparing and target coverage. Normal organ dysfunction risks – specifically to endocrine and cognitive impairment; reproductive; growth and cardiotoxicity– between both modalities were compared using relative risks (RR), odds ratio, predicted organ dysfunction or impairment after delivering a specified dose. Secondary malignancy risks (SMRs) based on International Commission on Radiological Protection (ICRP) 60 [12], organ-equivalent dose (OED) [13] and biologic effects of ionizing radiation (BEIR) VII [14] report were compared. Comparisons between lifetime attributable risk (LAR), ratio of LAR (RLAR) and RR of developing secondary malignancy between both radiation treatment modalities were also included.

Results

The search strategy identified 1049 studies, following review, 15 relevant studies were included in this analysis (Figure 1). No randomized controlled trial comparing Proton- and Photon-CSI were published in the specified search timeframe. Cohort, case-control studies, patient series and cross-sectional studies were included, with the majority of studies reporting on case studies. Full details of all included studies and their corresponding Downs and Black score can be found in Tables 2 (supplementary appendix A), 3 (supplementary appendix B) and 4 (supplementary appendix C).

Due to small sample size, heterogeneity in study objectives and analysis of the relationship between received dose and treatment outcomes, secondary data analysis of the data was not possible. Consequently, the results were aggregated in a qualitative manner to address the outcomes measures investigated by this review.

Dose distribution between proton and photon techniques

Eight of fifteen studies reported on dose distribution between Proton- and Photon-CSI concerning target conformity and homogeneity, and dose received by NTs [15–22] (Table 2 and supplementary appendix A). All eight studies reported better overall dose distribution for Proton-CSI when compared to Photon-CSI.

Table 1. Summary of inclusion and exclusion criteria.

Inclusion	Exclusion
• Studies published between 1990 and 2016 • Pediatric population between 2 and 18 yrs, diagnosed with medulloblastoma (high and low-risk) undergone post-surgical CSI with or without chemotherapy • Studies directly comparing Proton – and Photon-CSI and covering at least one of the following topics: normal tissue sparing and target coverage, normal organ dysfunction and second malignancy risks • Photon techniques could include three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and Tomotherapy • Proton techniques could include passive-scattered (PSPrT), spot-scanned proton therapy (SSPrT) and Intensity Modulated Proton Therapy (IMPT).	• Studies in abstract form only • Non-English articles • Patients with recurrent medulloblastoma disease and/or previous radiotherapy treatment

For the four studies [15,17,18,22] that compared target conformity and the three [15,17,18] that compared homogeneity between Proton- and Photon-CSI, inconsistent results were reported. Brodin et al. found greater target conformity in intensity modulated proton therapy (IMPT) than photon techniques [22]. Howell et al. [15] and Lee et al. [17] had consistent results; Proton-CSI was more homogeneous than Photon-CSI, and both modalities had similar conformity. Yet, Miralbell et al. [18] found similar homogeneity between proton therapy (PrT) and three-dimensional conformal radiation therapy (3DCRT), in a sample size of one.

Seven of eight studies examined NT dose. All seven articles demonstrated better sparing of most out-of field organs with Proton-CSI than 3DCRT and intensity modulated radiation therapy (IMRT) [15–21]. An exception was found for the lungs, where the dose difference between IMRT, 3DCRT and PrT was less pronounced (mean dose 3DCRT:3.2 Gy and PrT:1.8 Gy; 3CDRT:3.0 Gy and PrT: 2.2 Gy [20,21]) Two studies found similar in-field organ sparing between PrT and 3DCRT [15,17].

Normal organ dysfunction following proton and photon treatment

Six of fifteen studies compared normal organ dysfunction risks after Proton- and Photon-CSI [18–20,22–24] (Table 3 and supplementary appendix B). All six articles provided evidence to support that proton therapy had lower normal organ dysfunction risks than photon therapy in terms of stature loss (3DCRT: 23.2 cm and PrT: 6.8 cm) [18], cardiac toxicity (range of RRR (proton/photon) of cardiac toxicity: 0.12–0.24; RRR of cardiac toxicity in 3DCRT: 6.55 and RRR of cardiac toxicity in PrT: 0.15) [20,23], neurocognitive ([24] and reproductive [19] impairment, and overall increased normal tissue complication probability (NTCP) [22].

However, Miralbell et al. [18] argued that even though the vertebral body received lower dose from proton therapy than 3DCRT, stature loss was likely to arise from inhomogeneous dose, present in both modalities, to the vertebral body. Additionally, estimated cardiac toxicity risks were unreliable as NTCP parameters specific to medulloblastoma patients were unavailable [23]. Neurocognitive preservation varied greatly with Proton-CSI as the technique was more sensitive to CTV coverage constraints than Photon-CSI [24].

Risk of second malignancy following proton and photon treatment

Eight of fifteen articles [20–22,25–29] that compared SMR between Proton- and Photon-CSI, highlighted that Proton-CSI yielded lower SMR for most organs when compared to 3DCRT, IMRT and VMAT (Table 4 and supplementary appendix C). VMAT and IMRT led to highest SMR amongst all radiation techniques [21,22,29]. One study found similar SMR to the bones between PrT and 3DCRT [25]. Compared to 3DCRT, PrT significantly reduced lung dose for boys ($p = .015$) but not for girls ($p = .07$), hence, girls generally have higher SMR to the lungs compared to boys after PrT [20].

Discussion

CSI of pediatric medulloblastoma is associated with undesirable acute and late toxicity, as treatment involves large irradiation fields while patients are still in the developmental stage [30]. The evidence supporting the argument that Proton-CSI generally yielded plans with better dose distribution than Photon-CSI is compelling [15–22]. Earlier works by Miralbell et al., St Clair et al. and Lee et al. found that PrT superior at sparing out-of-field organs, such as the vertebral bodies, esophagus, heart and lungs, compared to 3DCRT and

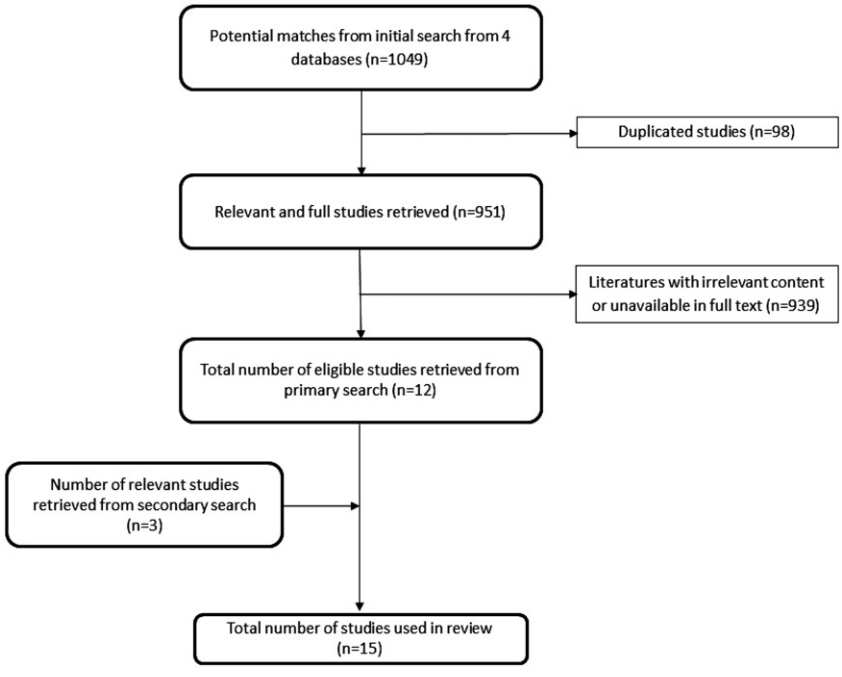

Figure 1. Flow diagram demonstrating search results.

Table 2. Summary of included studies comparing dose distribution of target and normal tissues (see supplementary appendix A for more detailed comparisons).

Author, year of study	Patient details	Radiation treatment details	Downs & Black score*	Conformity of plan	Homogeneity of plan	DVH of target volume	DVH of normal tissues		
Howell et al. (2012) [15]	$n = 18$ Age: 2–16 Yrs F-8, M-10	Technique: PSPrT, 3DCRT Treatment: CSI Px dose: 23.4 Gy-RBE	15 - good	3DCRT: 0.99 PSPrT: 0.99, p=.528	3DCRT: 1.05 PSPrT: 1.04, $p < .01$	Dmax ± SD: 3DCRT:28.13 ± 15.21 Gy PSPrT:26.05 ± 7.87 Gy-RBE, $p < .01$ V23.4 ± SD: 3DCRT:99.36 ± 1.04 Gy, PSPrT:99.23 ± 0.88 Gy-RBE, $p = .542$ V25 ± SD: 3DCRT:12.01 ± 9.87 Gy, PSPrT:1.72 ± 4.01 Gy-RBE, $p < .01$	Spinal cord Optic chiasm Cochlea Brain stem Esophagus; heart; kidney; liver; lungs and thyroid	V23.4 & V25 V23.4 V25 V23.4 V25 V23.4 & V25 V10; V15 & V20	3DCRT > PSPrT 3DCRT = PSPrT 3DCRT > PSPrT 3DCRT > PSPrT 3DCRT < PSPrT 3DCRT < PSPrT 3DCRT > PSPrT
St Clair et al. (2004) [16]	$n = 1$ Age: 3.6 Yrs M-1	Technique: 3DCRT; 3DCRT + IMRT; PrT Treatment: CSI + PF boost Px dose: 23.4 Gy-RBE to CSI, PF boost to 54 Gy-RBE	4 - poor	Not provided	Not provided	Not provided	Cochlea; pituitary; right TMJ and heart Hypothalamus Right parotid & right lung Pharynx Esophagus Stomach & transverse colon Right kidney	D5; D50 & D90 D5 & D90 D50 D5 D50 & D90 D5 D50 & D90 D5 D50 D90 D5 & D50 D90 D5 D50 & D90	3DCRT > IMRT > PrT 3DCRT > IMRT > PrT IMRT >3DCRT > PrT 3DCRT > IMRT > PrT IMRT >3DCRT > PrT IMRT >3DCRT > PrT 3DCRT > IMRT > PrT 3DCRT > IMRT > PrT 3DCRT > PrT > IMRT IMRT >3DCRT > PrT 3DCRT > IMRT > PrT IMRT >3DCRT > PrT 3DCRT > IMRT > PrT IMRT> 3DCRT > PrT
Lee et al. (2005) [17]	$n = 2$ Age: 3.5 & 16 Yrs F-1, M-1	Technique: 3DCRT, PrT Treatment: CSI + PF boost Px dose: 23.4 Gy-RBE to CSI, PF boost to 54 Gy-RBE	9 - fair	CI not provided but inferred from target coverage	HI not provided but inferred based on dose received by in-field organs: PrT superior to 3CDCRT	PF: 3DCRT: 100% received 54 Gy PrT: 96% received 54 Gy-RBE CSI: 3DCRT: 99% received 23.4 Gy PrT: 99% received 23.4 Gy-RBE	Cochlea Hypothalamus-pituitary Optic chiasm Eye Mandible Thyroid & kidney Heart & lung Liver	V20 ; V25 ; V35 ; V40 ; -V45 V10 V30 ; V40 ; V50 V20 V30 ; V40 ; V45 V20 V35 V10 ; V15 V10 ; V20 V10 ; V15 ; V20 V10 V20	3DCRT > PrT 3DCRT = PrT 3DCRT > PrT 3DCRT = PrT 3DCRT > PrT 3DCRT = PrT 3DCRT > PrT 3DCRT > PrT 3DCRT > PrT 3DCRT > PrT 3DCRT = PrT

(*continued*)

Table 2. Continued

Author, year of study	Patient details	Radiation treatment details	Downs & Black score*	Conformity of plan	Homogeneity of plan	DVH of target volume	DVH of normal tissues		
Mirabe-ll et al. (1997) [18]	$n = 1$ Age: 2.3 Yrs	Technique: SSPrT, 3DCRT Treatment: Spine Px dose: 30 Gy-RBE	7 - poor	Not provided	HI not provided but stated both techniques delivered doses homogenously	Numerical dose-volume not reported	Vertebral bodies Heart Liver	V50 & mean total dose D44 & mean dose D30 & mean dose	3DCRT > SSPrT 3DCRT > PSPrT 3DCRT > PSPrT
Perez-Andujar et al. (2013) [19]	$n = 1$ Age: 11 Yrs F-1	Technique: 3DCRT, IMRT, PrT Treatment: CSI Px dose: 23.4 Gy-RBE	9 - fair	Not provided	Not provided	Not provided	Equivalent dose (mean) (Sv) of ovaries was reported instead of DVH values. 3DCRT: 0.8 Sv, IMRT: 0.5 Sv, PrT: 0.2 Sv		
Zhang et al. (2014) [20]	$n = 17$ Age: 2–18 Yrs F-8, M-9	Technique: PSPrT, 3DCRT Treatment: CSI Px dose: 23.4 Gy-RBE	14 - fair	Not provided	Not provided	Not provided	Mean dose to stomach; thyroid; breast; heart; liver; lung; colon; prostate and bladder: 3DCRT > PSPrT		
Mu et al. (2005) [21]	$n = 5$ Age: 6–11 Yrs F-2, M-3	Technique: 3DCRT, IMRT, IMPT Treatment: Spine Px dose: 23.4 Gy-RBE	11 - fair	Not provided	Not provided	Not provided	Mean dose to thyroid; heart; esophagus and pancreas: 3DCRT > IMRT > PrT Mean dose to stomach; breast; liver; lung; spleen; kidney and abdominal cavity: IMRT >3DCRT > PrT		
Brodin et al. (2011) [22]	$n = 10$ Age: 4–15 Yrs	Technique: 3DCRT, VMAT, IMPT Treatment: CSI + PF boost Px dose: 36 Gy-RBE or 23.4 Gy-RBE to CSI, PF boost to 54 Gy-RBE	11 - fair	3DCRT: 0.61 VMAT: 0.73 IMPT: 0.89	Not provided	Not provided	Not provided		

F: female; M: male; Yrs: years; CSI: craniospinal irradiation; PF: posterior cranial fossa; Px: prescription; RBE: relative biological effectiveness; DVH: dose volume histogram; 3DCRT: three-dimensional conformal radiation therapy; IMRT: intensity modulated radiation therapy; VMAT: volumetric modulated arc therapy; PrT: proton therapy; PSPrT: passive scattered proton therapy; SSPrT: spot scanned proton therapy; IMPT: intensity modulated proton therapy; HI: homogeneity index; CI: conformity index; Sv: sievert; SD: standard deviation; TMJ: temporomandibular joint.
*Downs and Black scoring: articles scoring between 0 and 201 were rated as 'Poor', 8–14 as 'Fair', 15–21 as 'Good' and 22–28 as 'Excellent' [11].

Table 3. Summary of included studies comparing normal organ dysfunction risks (see supplementary appendix B for more detailed comparisons).

Author, year of study	Patient details	Radiation treatment details	Downs and Black score*	Relative risks (RR)	Ratio of RR (RRR)	Odds ratio	Organ dysfunction
Perez-Andujar et al. (2013) [19]	$n = 1$ Age: 11 Yrs F-1	Technique: 3DCRT, IMRT, PrT Treatment: CSI Px dose: 23.4 Gy-RBE	9 - fair	Not provided	RRR of premature ovarian failure Ovary set / $RRR_{3DCRT/PrT}$ / $RRR_{IMRT/PrT}$ Nominal 3.00 2.06 1 1.71 7.75 2 9.58 8.16 3 3.13 4.68 4 2.18 1.49 5 3.50 2.87	Not provided	Not provided
Mirabell et al. (1997) [18]	$n = 1$ Age: 2.3 Yrs	Technique: SSPrT, 3DCRT Treatment: Spine Px dose: 30 Gy-RBE	7 - poor	Not provided	Not provided	Not provided	Predicted stature loss: 3DCRT: 23.2 cm SSPrT: 6.8 cm
Zhang et al. (2013) [23]*	$n = 1$ Age: 4 Yrs M-1	Technique: PSPrT, 3DCRT Treatment: CSI Px dose: 23.4 Gy-RBE	8 - fair	Cardiac Toxicity PSPrT: 1.28 3DCRT: 8.39	RRR_{3DCRT} of cardiac toxicity = 6.55 RRR_{PSPrT} of cardiac toxicity = 0.15	Not provided	Not provided
Brodin et al. (2011) [22]	$n = 10$ Age: 4–15 Yrs	Technique: 3DCRT, VMAT, IMPT Treatment: CSI + PF boost Px dose: 36 Gy-RBE or 23.4 Gy-RBE to CSI, PF boost to 54 Gy-RBE	11- fair	Not provided	Not provided	Not provided	NTCP was presented graphically only: 3DCRT > VMAT > IMPT
Blomstra-nd et al. (2012) [24]	$n = 6$ Age: 6–11 Yrs	Techniques: 3DCRT, IMRT, VMAT, IMPT Treatment: WBRT Px dose: 36 Gy-RBE or 23.4 Gy-RBE	9 - fair	Not provided	Not provided	Px dose / IMPT/IMRT V95%=98% / IMPT/IMRT V95%=95% / IMRT/VMAT V95%=98% / IMRT/VMAT V95%=95% Task-efficiency: 36 Gy 0.64 0.28 0.77 0.68 23.4 Gy 0.75 0.44 0.84 0.78 Organization: 36 Gy 0.73 0.43 0.83 0.76 23.4 Gy 0.82 0.56 0.88 0.83 Memory: 36 Gy 0.87 0.67 0.92 0.88 23.4 Gy 0.91 0.76 0.94 0.92	Predicted risks of memory impairment after 23.4 Gy: 3DCRT: 47% VMAT: 44% IMRT: 41% IMPT: 33%
Zhang et al. (2014) [20]**	$n = 17$ Age: 2–18 Yrs F-8, M-9	Techniques: PSPrT, 3DCRT Treatment: CSI Px dose: 23.4 Gy	14 -fair	Actual figures not reported	Range of RRR (proton/photon) of cardiac toxicity = 0.12–0.24 ($p < .001$)	Not provided	Not provided

F: female; M: male; Yrs: years; CSI: craniospinal irradiation; PF: posterior cranial fossa; Px: prescription; RBE: relative biological effectiveness; DVH: dose volume histogram; 3DCRT: three-dimensional conformal radiation therapy; IMRT: intensity modulated radiation therapy; VMAT: volumetric modulated arc therapy; PrT: proton therapy; PSPrT: passive scattered proton therapy; SSPrT: spot scanned proton therapy; IMPT: intensity modulated proton therapy; RBE: relative biological effectiveness; RR: relative risk; RRR: ratio of relative risk; NTCP: risk normal tissue complication probability; WBRT: whole brain radiation therapy

*Downs and Black scoring: articles scoring between 0 and 7 were rated as 'Poor', 8–14 as 'Fair', 15–21 as 'Good' and 22–28 as 'Excellent' [11].

**Patient reported in study [23] was also included as part of the analysis in study [20].

Table 4. Summary of included studies comparing secondary malignancy risks (see supplementary appendix C for more detailed comparisons).

Author, year of study	Patient details	Radiation treatment details	Downs and Black score*	Lifetime attributable risk (LAR)	Ratio of LAR (RLAR)	Risk of secondary cancer	Relative cancer risks/absolute lifetime risk (ALR)
Mu et al. (2005) [21]	$n = 5$ Age: 6–11 Yrs F-2, M-3	Technique: 3DCRT, IMRT, IMPT Treatment: Spine Px dose: 23.4 Gy-RBE	11 - fair	Not provided	Not provided	3DCRT: 0.198 IMRT:0.303 IMPT: 0.034 (0.04 if account for neutrons)	Not provided/not provided
Zhang et al. (2014) [20]*	$n = 17$ Age: 2–18 Yrs F-8, M-9	Technique: PSPrT, 3DCRT Treatment: CSI Px dose: 23.4 Gy-RBE	14 - fair	Mean LAR incidence for stomach; colon; liver; lung; breast; prostate; bladder and thyroid: 3DCRT > PSPrT	$RLAR_{(proton/photon)} \pm SD$ for 2nd cancer incidence = 0.15 ± 0.04 ($p < .001$) Correlation between RLAR of 2nd cancer incidence with age: $r = -0.74$ ($p < .001$)	Not provided	Not provided/not provided
Stokkevag et al. (2014) [25]	$n = 6$ Age: 5–11 Yrs F-3, M-3	Technique: 3DCRT, PSPrT, IMPT Treatment: CSI Px dose: 23.4 Gy-RBE	10 - fair	LAR for lungs, thyroid, colon, bladder, stomach and liver: Protons < photons techniques	Not provided	Not provided	Relative cancer risks: Relative risk of cancer based on OED: PSPrT < photon techniques, except for the bones Absolute lifetime risk: not provided
Mirabell et al. (2002) [26]	$n = 1$ Age: 3 Yrs M-1	Technique: 3DCRT, IMRT, SSPrT Treatment: CSI (spinal theca) Px dose: 36 Gy-RBE	5 - poor	Not provided	Not provided	Absolute yearly rate of secondary cancer incidence for Stomach; esophagus; colon; thyroid; bone and connective tissues; leukemia and all secondary cancers: 3DCRT > IMRT > SSPrT Breast: 3DCRT = IMRT = SSPrT Lung: 3DCRT = IMRT > SSPrT	Relative risk of secondary cancer: (IMRT/3DCRT) = 0.6 (SSPrT/3DCRT) = 0.07 Absolute lifetime risk: not provided
Taddei et al. (2015) [27]	$n = 1$ Age: 13 Yrs F-1	Technique: PSPrT, 3DCRT Treatment: CSI Px dose: 23.4 Gy-RBE	10 - fair	Not provided	RLAR (Proton/Photon) for secondary cancer incidence: Non-melanoma skin cancer = 1 Leukemia = 0.81 Thyroid = 0.07 Other solid = 0.67 Bladder = 0.17 Ovary = 0.15 Uterus = 0.26 Breast = 0.25 Lung = 0.44 Liver = 0.17 Colon = 0.07 Stomach = 0.05	Not provided	Relative cancer risk: Not provided Absolute lifetime risk: 3DCRT: Highest ALR for thyroid cancer, non-melanoma skin cancer, other solid cancer and lung cancer, PSPrT: Highest ALR for non-melanoma skin cancer, other solid cancer and lung cancer
Zhang et al. (2013) [28]**	$n = 1$ Age: 4 Yrs M-1	Technique: PSPrT, 3DCRT Treatment: CSI Px dose: 23.4 Gy-RBE	8 - fair	PSPrT: 11.6%; 3DCRT: 138%	RLAR (Proton/Photon) for secondary cancer incidence: 0.083 (95% confidence interval 0.081–0.085).	Not provided	Relative cancer risk: ratio of relative risk (proton/photon) 15 Yrs / 30 Yrs / 45 Yrs / 60 Yrs Stomach 0.31 / 0.38 / 0.46 / 0.52 Colon 0.08 / 0.10 / 0.13 / 0.16 Liver 0.12 / 0.17 / 0.23 / 0.28 Lung 0.18 / 0.24 / 0.30 / 0.36 Prostate 0.38 / 0.56 / 0.67 / 0.74 Bladder 0.11 / 0.17 / 0.23 / 0.28 Thyroid 0.06 / 0.06 / 0.06 / 0.06 Absolute lifetime risk: Not provided
Brodin et al. (2012) [29]	$n = 10$ Age: 4–15 Yrs	Technique: 3DCRT, VMAT, IMPT Treatment: CSI + PF boost Px dose: 36 Gy- CSI, PF boost – 54 Gy	11- fair	36 Gy-RBE to CSI and PF boost to 54 Gy-RBE: 3DCRT: 33% VMAT: 40% IMPT: 18%	Not provided	3DCRT = 33%, VMAT = 40%, IMPT = 18%	Not provided/not provided

(*continued*)

Table 4. Continued

Author, year of study	Patient details	Radiation treatment details	Downs and Black score*	Lifetime attributable risk (LAR)	Ratio of LAR (RLAR)	Risk of secondary cancer	Relative cancer risks/absolute lifetime risk (ALR)
Brodin et al. (2011) [22]	$n = 10$ Age: 4–15 Yrs	Technique: 3DCRT, VMA, IMPT Treatment: CSI + PF boost Px dose: 36 Gy-RBE or 23.4 Gy-RBE to CSI, PF boost to 54 Gy-RBE	11- fair	Not provided	Not provided	23.4 Gy-RBE: 3DCRT = 45%; VMAT = 56%; IMPT = 7% 36 Gy-RBE: 3DCRT = 54%; VMAT = 71%; IMPT = 9%	Not provided/not provided

F: female; M: male; Yrs: years; 3DCRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; PrT: proton therapy; PSPrT: passive scattered proton therapy; SSPrT: spot scanned proton therapy; IMPT: intensity modulated proton therapy; CSI: craniospinal irradiation; PF: posterior cranial fossa; Px: prescription; OAR: organ at risk; RBE: relative biological effectiveness; ALR: absolute lifetime risk; LAR: lifetime attributable risk; RLAR: ratio of lifetime attributable risk; SD: standard deviation; OED: organ equivalent dose
*Downs and Black scoring: articles scoring between 0 and 7 were rated as 'Poor', 8–14 as 'Fair', 15–21 as 'Good' and 22–28 as 'Excellent' [11].
**Patient reported in study [28] was also included as part of the analysis in study [20].

IMRT [16–18]. Miralbell et al. [18] studied the spinal irradiation component for a single pediatric medulloblastoma patient and reported that Proton-CSI had an advantage over 3DCRT, as Proton-CSI reduced dose to the vertebral body and avoided dose deposition to the heart and liver. However, this result should be interpreted with caution due to the small sample size.

St Clair et al. [16] highlighted that out-of-field organ sparing is subject to a defined target volume. Though Proton-CSI was able to deliver near-zero percent dose to these organs, the esophagus was an exception, as D5% of the posterior esophagus with PrT (99%) surpassed IMRT (66.6%) and 3DCRT (88.8%) [16]. Since, the target volumes of 3DCRT and PrT were at the posterior surface of the vertebral body and anterior surface of the vertebral body (both the anterior and posterior vertebrae were included to preclude growth differential), respectively, the posterior esophagus was located in the steep dose gradient of the proton beam and thus received higher than expected dose. Likewise, posterior vertebral body would receive a greater dose if target volume was increased to account for greater target positional uncertainties [18]. However, these results are not generalizable due to poor study power. On the contrary, the largest study to date by Howell et al. revealed that PrT significantly improved all NT sparing even with age-specific target volumes [15].

Interestingly, two studies concluded that mean lung doses were not significantly lower in PrT, relative to Photon-CSI [20,21]. In particular, PrT significantly reduced lung dose, relative to 3DCRT, for boys ($p = .015$) but not for girls ($p = .07$) [20]. Generally, girls are physically smaller than boys of similar age, which meant larger proportion of their lungs was irradiated and resulted in insignificant dose-volume difference between Proton- and Photon-CSI for the population as a whole. This implied that NT sparing could be effected by size/gender differences.

In-field organ sparing, mainly cranial structures, were generally similar between both modalities [15,17]. However, upon examination of higher dose levels (V25–V40), Proton-CSI superseded Photon-CSI despite the addition of a posterior fossa boost. This was attributed to improved plan homogeneity with PrT, where treated volume received smaller volumes of high doses with PrT [15,22].

Miralbell et al. concluded similar target homogeneity between PrT and 3DCRT [18]. However, the observation should be treated with caution as it was based on visual observation of the target DVH and a sample size of one. Objective calculation of the homogeneity index (HI) by Howell et al. [15] revealed significant superior target homogeneity with PrT (HI = 1.04) than 3DCRT (HI = 1.05, $p = .000487$), which was consistent with other studies [17,22].

Conflicting conclusions on target conformity were identified. While Howell et al. [15] found similar conformity index (CI) between PrT and 3DCRT (both CI = 0.99, $p = .528$), Brodin et al. [22] found better target conformity with PrT (CI = 0.89) than VMAT (CI = 0.73) and 3DCRT (CI = 0.61). This inconsistency was likely because of CI calculation differences. The former study calculated CI according to RTOG guidelines [31] while the latter was based on the study by Paddick [32], which accounted for spatial overlap of the target and

prescription volume. Though no independent studies have been conducted to compare accuracy between both formulae, the latter formula highlighted the need for visual inspection for plan evaluation. It should also be noted that CI and inhomogeneity coefficient may not be the most appropriate parameters to compare these large target volumes but in the absence of the included publications using other alternatives, it was used for direct comparison purposes.

Improvements in NT sparing led to reduced late normal organ dysfunction risks with PrT, in terms of stature loss [18], cardiac toxicity [20,23], neurocognitive [24] and reproductive [19] impairment and overall increased NTCP [22]. However, better organ sparing may not translate into reduced normal organ dysfunction if NTs received inhomogeneous dose. A historical study concluded that doses below 10 Gy failed to cause permanent vertebral deformity [33]. Stature loss was weakly related to heterogeneous vertebral body dose [34]. Thus, the advantage of reduced stature loss with PrT (6.8 cm) compared with 3DCRT (23.2 cm), predicted by vertebral dose, may not exist as both modalities delivered vertebral doses heterogeneously [18]. Moreover, several studies reported that age of exposure and chemotherapy were also related to vertebral deformity [35–38]. Hence, PrT might not confer better growth preservation due to the multifactorial nature of stature loss.

PrT reduced RR of cardio-toxicity as it delivers lower equivalent dose (PrT = 0.47 Sv, 3DCRT = 12.31 Sv) to the heart [20,23]. However, RR of cardio-toxicity was derived from linear dose-response model and thus should be treated with caution. Accuracy of the linear model is questionable, as the authors who formulated the equation in a prospective study, found that actual cardio-mortality was five-fold more than expected [39]. This discrepancy could be attributed to confounders like smoking. [40] Similarly, NTCP relative seriality [41] and Lyman models [42] predicted lower cardio-toxicity risk with PrT than Photon-CSI [23]. But, its reliability can be undermined due to the lack of data linking radiation dose and incidence of cardio-toxicity for medulloblastoma patients [23]. This highlights the need for more suitable risk models to gain a more accurate insight on the risks following PrT.

Neurocognitive preservation is important as impairment is a strong predictor of poor QOL [43]. Blomstrand et al. [24] found lower neurocognitive impairment risk with PrT compared to 3DCRT, IMRT and VMAT. Nevertheless, cognitive-impairment risk following PrT fluctuates because of its high sensitivity to CTV constraint changes. When CTV V95% was constrained from 95 to 98%, cognitive-impairment risk after PrT increased markedly, but potential neurocognitive preservation could be attainable if hippocampal-sparing was employed [24]. For traditional CSI treatment where the entire cranial contents are uniformly irradiated, PrT and Proton-CSI may yield similar neurocognitive dysfunction since the hypothalamus would receive 100% of the prescribed dose [15,17]. While one might argue that PrT could better spare neural structures from additional doses during posterior fossa boost, studies found no differences in the high-dose sparing of the chiasm (PrT and IMRT: V30 = 0%) and hypothalamus-pituitary (PrT and IMRT: V30 = 0%) between PrT and IMRT [17]. Therefore, PrT is not necessarily superior to a well-designed IMRT plan in this context [44]. Nonetheless, the gradual trend away from whole-brain irradiation and toward tumor-focused irradiation [45] might further establish the advantage of neurocognitive preservation with PrT.

Perez-Andujar et al. [19] found that PrT reduced ovarian dose and premature ovarian failure (POF) risks compared with 3DCRT and IMRT, regardless of ovary position. Yet this study failed to consider POF from another factor; while PrT conferred POF reduction due to reduced direct irradiation of the ovaries [46], POF could also be indirectly caused by hypothalamic-pituitary axis irradiation within the cranial field [47] and as such, PrT may still result in POF. However, it was noted that POF, regardless of radiation modality, would pose a risk if hypothalamic-pituitary dose exceeds 30 Gy [48]. This primarily affects high-risk medulloblastoma patients where whole-brain is prescribed between 36 and 39.6 Gy [49]. A recent study by Eaton et al. [50] evaluated the endocrine outcomes in both Proton-CSI ($n = 40$) and Photon-CSI ($n = 37$) patients, and while it did not meet the inclusion criteria for this review due to the age of the study population exceeding 18 years it noted that there was statistically significant reduction in risk of hypothyroidism, sex hormone deficiencies and the requirement for any endocrine replacement therapy in those patients who were treated with Proton-CSI. Conversely, they also reported proton-CSI resulted in greater height standard deviation scores and suggested this may indicate a difference in the effect of radiotherapy modality on growth hormone rather than a direct result of vertebral body irradiation.

Substantial evidence points to greater SMR after Photon-CSI than Proton-CSI [20–22,25–29], with 3DCRT reported to increase SMR by 2–15 times when compared to PrT [21,22,25,26,28,29]. However, direct inter-study comparison of SMR was complicated by the variations in risk models used. Several studies [51,52] have argued that SMR models introduced in the BEIR VII report were developed for organs receiving low doses, and have proposed other dose-risk models. Yet, new risk models may be inaccurate if they contain large unknown errors and even then, it is worthwhile to estimate SMR even at low doses as secondary malignancies can occur without any threshold dose [14]. Furthermore, three articles [22,25,29] that derived SMRs based on OED [13] yielded inconsistent results reporting lower SMRs with PrT, relative to 3DCRT, ranged between 2 and 8 times. This was attributed to different dose-response models used; Stokkevag et al. [25] used the linear-exponential model while Brodin et al. [22] used the plateau model. Brodin et al. [29] conducted a similar study but in a larger cohort and the OED dose-response model used was organ-dependent; heart and lungs followed a linear dose-response while the thyroid followed a linear-exponential dose-response. Additionally, the OED concept was based on secondary cancer data from Hodgkin's lymphoma patients after radiation therapy; hence, uncertainties are expected when it was applied to the medulloblastoma population. Although no consensus on the standard SMR model was established, the results were clear – Photon-CSI conferred higher SMR than PrT.

It should be noted that age influences target volume definition, subsequently affecting SMR. Stokkevag et al. found

that the OED-derived SMR for bones, following PrT, only reduced marginally. This might be because age-specific target volumes was employed, with the entire vertebral body was defined for patients below 15 years old receiving PrT [25]. The OED for the vertebrae was lower for patients above 15 years old, where spinal target includes the spinal canal and extends 2–3 mm into the vertebral body [53], creating a sharp dose fall-off beginning at the anterior spinal canal rather than at the anterior vertebral bodies [15]. Hence, SMR for the vertebrae would be much lower for patients over 15 years old receiving PrT when compared with photon therapy.

Mu et al. [21] noted that the mean lung dose was not significantly reduced with PrT. This was later supported by Zhang et al. [20] and Taddei et al. [27] who concluded that SMR after PrT was generally reduced with the exception of the lungs. Girls were found to have higher LAR of lung cancer than boys resulting from a greater proportion of their lungs received more dose due to their smaller physical stature, as mentioned previously. Putting it on a broader perspective, SMR should be recognized as dose-volume dependent [54], hence patient size, rather than gender, should be one of the factors that dose models from BEIR VII report should account for.

Documented secondary malignancies following CSI were predominantly brain cancer [55]. It could be argued, therefore, that such secondary malignancies would be unavoidable as the neural-axis receives similar dose in Proton-CSI and Photon-CSI. Hence, PrT might not reduce SMR compared to Photon-CSI, even with reduced exit-dose [44].

Eaton et al. [56] further analyzed the cohort of pediatric patients previously discussed and noted that there was no incident of a second malignancy in the Proton-CSI cohort ($n = 45$) but three patients treated using Photon-CSI ($n = 43$) developed a secondary malignancy. They cautioned drawing conclusions on this due to their small patient numbers and lack of sufficient follow up.

While cost-effectiveness was not included in this review, it would be remiss not to mention it in the context of comparing both modalities. Proton therapy is undoubtable associated with higher initial infrastructural costs when compared to photon therapy; therefore, it is important to balance the clinical benefits with the related treatment costs. Lundkvist et al. [57] simulated a cost analysis of Protons-CSI in pediatric medulloblastoma taking in to account cost, gained life years and QOL and concluded that Proton-CSI was associated with cost savings of €23,600 and 0.68 additional quality-adjusted life-years per patient when compared to conventional radiotherapy. The greatest cost savings were in relation to reductions in intelligence quotient loss and growth hormone deficiency that would result from using Proton-CSI. As with the other aspects in this review, the lack of long-term data makes it difficult to draw firm conclusions from the literature.

It must be recognized that late toxicity following Proton-CSI can only be predicted at this stage. Since reduced toxicity may not translate to better survival, should Photon-CSI remain the ethical, cost-effective and readily available standard of care for pediatric medulloblastoma patients? This question can only be answered through a randomized controlled trial comparing both treatment modalities [44].

To conclude, PrT revealed advantage in NT sparing, normal organ dysfunction and secondary malignancy risks when compared to various photon techniques Target coverage between both radiation modalities were either similar or better with PrT and PrT improved out-of-field organ sparing normal organ dysfunction was generally lower with PrT due to increased NT sparing. However, dysfunction can arise from indirect irradiation and predicted risks can be altered according to survivor's future lifestyle habits. All studies consistently pointed to lower SMR with Proton-CSI than Photon-CSI. However, the degree of clinically meaningful benefit with Proton-CSI from a toxicity and SMR standpoint is subject to uncertainty because of the absence of convincing long-term clinical evidence to determine both tumor control and toxicity. This review serves as a preliminary address on Proton-CSI for pediatric medulloblastoma patients in the absence of long-term results from prospective studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

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