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ORIGINAL ARTICLE

Neurocognitive impairment following proton therapy for paediatric brain tumour: a systematic review of post-therapy assessments

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Abstract

Background Proton therapy (PT), frequently utilised to treat paediatric brain tumour (PBT) patients, eliminates exit dose and minimises dose to healthy tissues that theoretically can mitigate treatment-related effects including cognitive deficits. As clinical outcome data are emerging, we aimed to systematically review current evidence of cognitive changes following PT of PBT.

Materials and methods We searched PubMed and Scopus electronic databases to identify eligible reports on cognitive changes following PT of PBT according to PRISMA guidelines. Reports were extracted for information on demographics and cognitive outcomes. Then, they were systematically reviewed based on three themes: (1) comparison with photon therapy, (2) comparison with baseline cognitive measures, to population normative mean or radiotherapy-naïve PBT patients and (3) effects of dose distribution to cognition.

Results Thirteen reports (median size (range): 70 (12–144)) were included. Four reports compared the cognitive outcome between PBT patients treated with proton to photon therapy and nine compared with baseline/normative mean/radiotherapy naïve from which two reported the effects of dose distribution. Reports found significantly poorer cognitive outcome among patients treated with photon therapy compared with proton therapy especially in general cognition and working memory. Craniospinal irradiation (CSI) was consistently associated with poorer cognitive outcome while focal therapy was associated with minor cognitive change/difference. In limited reports available, higher doses to the hippocampus and temporal lobes were implicated to larger cognitive change.

Conclusion Available evidence suggests that PT causes less cognitive deficits compared with photon therapy. Children who underwent focal therapy with proton were consistently shown to have low risk of cognitive deficit suggesting the need for future studies to separate them from CSI. Evidence on the effect of dose distribution to cognition in PT is yet to mature.

Keywords Cognition · Paediatric cancers · Brain tumours · Proton therapy

Abbreviations

PT	Proton therapy
PBT	Paediatric brain tumour
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CSI	Craniospinal irradiation
WISC	Wechsler Intelligence Scale for Children

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Introduction

Among long-term paediatric brain tumour (PBT) survivors, a decline in core foundational cognitive ability including in memory, working memory, attention and information processing speed is an important consequence of the disease and treatment [1, 2]. The decline may affect the quality of life including difficulties in social functioning, employment and education attainment [3–5]. Children have disproportionately higher risks of impairment due to the rapid development of

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glial cells during childhood. Thus, improving therapies to mitigate the decline is paramount.

As there are multitudes of evidence suggesting that higher radiation dose to normal brain tissue is associated to greater cognitive decline in photon-based therapy [6, 7], proton therapy (PT) which eliminates exit dose and can be tailored to minimise dose to normal brain tissues is a promising solution [8–11] . Merchant et al. produced a theoretical quantitative model which predicted significant neuro-sparing benefit of PT owing to a lower volume of temporal lobes and cerebrum receiving high dose [12].

However, PT is up to 2.4 times more expensive than photon therapy and may not be an affordable option for many [13–15]; thus, questions whether the cost is justified in terms of clinically meaningful and evidence-based improvement of treatment outcomes are important [16, 17]. While dosimetric analyses have consistently shown the potential neuro-sparing benefit of PT for PBT patients based solely on dosimetric advantage alone [8, 9, 11, 18, 19], yet, there appear to be few reports presenting actual clinical cognitive outcomes. The limited availability of PT in the past may be the reason for the sparse empirical evidence of the cognitive benefit. However, as more centres are offering PT as a standard for PBT patients, the uncertainty that still lingers after years of PT introduction may come to an end as more clinical results mature. In this study, we aimed to systematically review the cognitive changes following proton therapy of paediatric brain tumour patients.

Materials and methods

Systematic review protocol and eligibility criteria

The systematic review protocol and methodology established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were utilised [20–22]. Original research manuscripts were evaluated for inclusion or exclusion based on PICOS criteria detailed in Table 1. The PICOS framework was used to develop literature search strategies by systematically determining the inclusion based on patient population, intervention, comparison, outcome and study design. Reports fulfilling all five criteria were included. Excluded studies were reported based on the first PICOS criterion not fulfilled.

Search strategy and selection process

Electronic databases (National Center for Biotechnology Information (PubMed) and Scopus) were systematically searched to identify relevant articles. Keywords and search strings used are detailed in the Supplementary Material A. In the first phase, articles were reviewed in increasing specificity via the title, abstract, then finally, via full text by NY and HAM independently. In the second phase, bibliographic references and citations of the included studies were extracted from Scopus and hand searched for additional eligible studies based on the assumption that relevant studies cited or were cited by other related studies. Despite a small chance of publication bias that is expected to be prevented in the first phase, we have confidence in the robustness of this two-step method to ensure no omission of relevant studies. No publication date or publication status restriction was imposed. Discrepancies in the results of the selection were deliberated in team meetings. Where more than one reports of a study existed or where the independence of cohorts is questionable, reports of which subjects were a complete subset of a later report were excluded. Study search and selection were completed on 5 February 2020.

Quality assessment

We used an assessment tool from the National Heart, Lung and Blood Institute, Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, to assess the quality of included studies.

Table 1 PICOS criteria for inclusion in systematic review

Criteria	
P—patient	Patients treated with paediatric brain tumours (PBT) regardless of age at follow-up. Threshold age is 21. In a mixed population, it should not consist of more than 10% adult patients (age > 21).
I—intervention	Proton therapy (PT).
C—comparison	pre- and post-PT or between post-PT and healthy controls or between post-PT and normative means or between post-PT and post-photon therapy
O—outcome	Any cognitive measures.
S—type of study	Exclude studies with no statistical comparisons (case study or case series), reviews or consisting of less than 10 patients.

Data review and extraction

Upon finalisation of article selection, both authors performed data extraction together. Information was extracted into spreadsheets and included details of the articles, patients, proton therapy dose regime and technique and measures for cognitive changes. Data on cognition following PT for PBT, comparison with photon-based radiotherapy or to baseline cognitive measures, population normative mean or radiotherapy-naïve patients, dose-effect and predictors of cognitive outcomes were extracted.

Results

Study selection and quality assessment

The database queries produced 1248 and 131 records from PubMed and Scopus, respectively (Fig. 1, Supplementary A). After removal of duplicates, 1275 reports were reviewed for inclusion and 13 met the inclusion criteria. One report [23] was a subset of another report [24], thus, excluded. In the second phase, where references and citations of the previously selected reports were reviewed using Scopus that is a source-neutral abstract and citation database, 608 articles were reviewed, and one recently published report was included.

Even though some included studies reported longitudinal comparisons, they are not compulsory for inclusion. Thus, a less stringent quality apparatus, Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, was utilised. Generally, studies have a reasonable quality with most reported lower accrual rate than the pool of eligible persons due to the lack of neurocognitive assessment available (Supplementary B). Except for Peterson et al. [25], all others reported the effect of exposures (i.e. dose or treatment fields). Sample size and calculations were rarely mentioned due to the retrospective or hypothesis-generating nature of most studies.

Characteristics of included studies

Table 2 summarises the characteristics of the selected studies [25–34]. Only two studies reported prospectively accrued patients while the rest reported retrospective cohorts [30, 34]. The publication dates ranged from 2013 to 2020, which reflect the recency of PT introductory into widespread practice. The reports included 651 paediatric patients irradiated to the brain

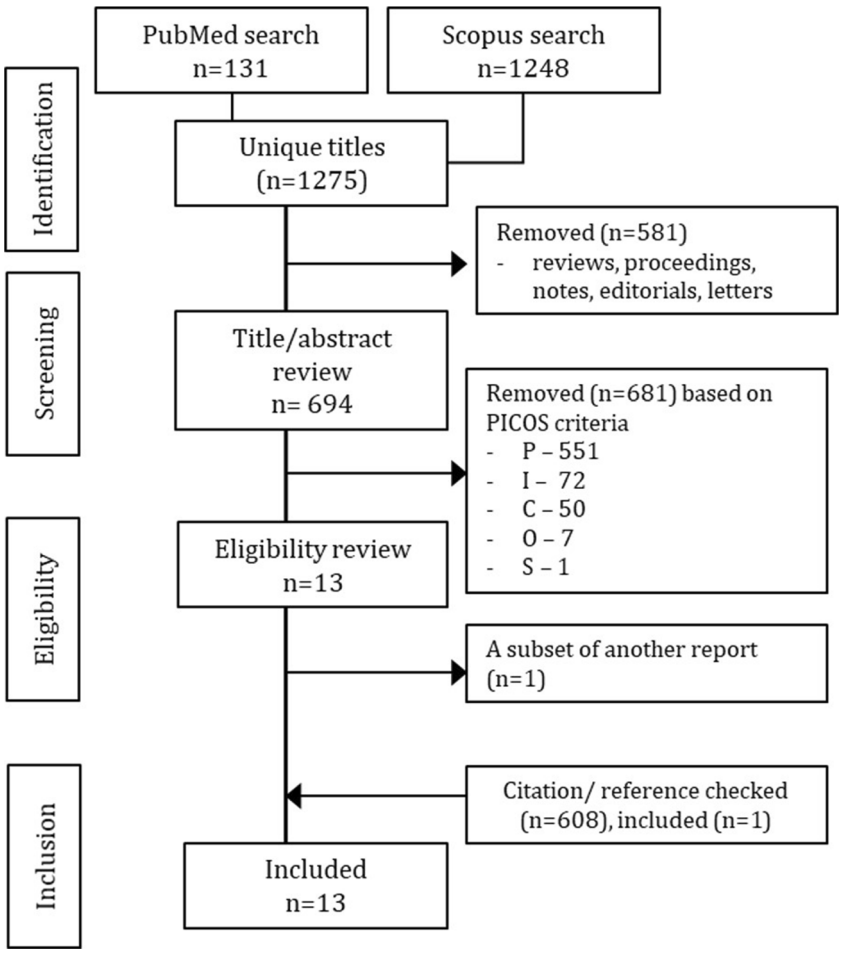

Fig. 1 Identification for inclusion based on PRISMA. Eligibility was determined using PICOS criteria

Table 2 Study characteristics

Author, year	Study design	Total no. of patients	Evaluable: proton	Evaluable: non-proton	% Female	Tumour type	% CSI	Dose (Gy)	Age at treatment/ baseline testing/ diagnosis	Time from treatment to neurocognitive evaluation	Neurocognitive tests
Antonini, 2017	Retrospective	39	37	0	35.9	Glioma (10), medulloblastoma/PNET (14), germ cell tumour (9), craniopharyngioma (2)	53	CSI: 55.80 (45–55.8), focal: 50.40 (45–60)	At treatment—CSI: 10.90 (3.01–15.54), focal: 9.91 (1.56–16.27)	CSI: median 2.92 (1.15–7.30), focal: 2.20 (1.07–6.91)	CPT-II, D-KEFS, VMI–6th ed
Greenberger, 2014	Retrospective	32	12	9 (photon and proton)	46.9	low grade glioma (32)	0	52.2 (46.8–54)	At treatment—11.0 (2.7–21.5)	4.5 (1.2–8.1)	WISC-IV and analogous scores from WISC-III, WPPSI-III, WASI, WAIS-III, and WAIS-IV
Gross, 2019	Retrospective	125	58	67	40.8	Glioma (16), medulloblastoma/PNET (67), ependymoma (16), germ cell (15), craniopharyngioma (6), other (5)	52.8	CSI: 23.4 or 36, primary not detailed	At treatment photon: 7.35 (4.57–11.03); proton: 8.50 (5.75–11.81)	Photon: 6.7 (IQR 3.6–9.7), proton 2.6 (IQR 1.4–3.6)	WASI 2nd ed., WISC 4th/5th ed., WAIS 3rd/4th ed., CMS, WRAML 2nd ed., VMI, WIAT 3rd ed., WJTA 3rd/4th ed.
Kahalley, 2016	Retrospective	150	90	60	42	Glioma (28), medulloblastoma/PNET (62), ependymoma (17), germ cell tumour (20), other (23)	54.6	Focal - Photon 54.0 (30.6–59.4), PBRT 54.0 (30.0–60.0); CSI - photon 23.4 (21.0–39.6), PBRT 23.4 (21.0–39.6); tumour bed boost - photon: 55.8 (44.4–55.8), PBRT: 54.0 (30.0–55.8)	At treatment photon-mean 8.1 ± 3.9 (1.2–18.0); proton-mean 9.2 ± 4.1	Photon-mean 5.4 (SD 3.3), proton-mean 2.7 (SD 1.9)	WSIC, WJA, LIPS
Kahalley, 2019	Prospective	93	53	40 (no RT, surgery only)	48.3	Glioma (49), medulloblastoma/PNET (18), germ cell tumour (6), craniopharyngioma (8)others (6)	41.5	CSI (tumour) : 54.0 (45.0–54.0), focal 50.4 (30.0–59.4); CSI: 23.4 (15.0–36.0)	At treatment: CSI: 10.1 (4.0–18.2), focal: 9.2 (3.4–17.1), surgery only: 9.7 (2.9–18.6)	CSI: 2.8 (0.8–5.4), focal: 2.9 (0.5–6.1), surgery only: 3.1 (1.0–6.0)	WSIC
Kahalley, 2020	Retrospective	79	37	42	32.9	Medulloblastoma	100	Photon: CSI: 23.4 (15.0–39.4), tumour 55.8 (51.0–59.4); proton: CSI: 23.4 (15.0–36.0), tumour 54.0 (51.0–55.8);	At baseline mean (SD): photon—9.5 (3.1); proton 9.3 (3.0)	Photon mean (SD): 4.8 (2.1); proton: 3.7 (3.4)	WSI, WJCA-3rd ed., SBI 5th ed.
MacDonald, 2013	Retrospective	70	14	0	53	Ependymoma (70)	0	55.8 (50.4–60.0)	At diagnosis: 38 months (3 months to 20 years)	Mean (range) 2.05 (1.0–4.5)	BSID 2nd ed., WISC 4th ed., WPPSI – 3rd ed., WAIS 3rd ed.
Park, 2017	Retrospective	34	20	0	32.4	Germ cell tumour (34)	55.9	39.6 (30.0–55.8)	At diagnosis: 12.0 (7.0–18.1)	3.7 (0.5–8.0)	Korean-WISC, Korean-WAIS, Rey-Kim Memory Test, Kim's Frontal

Table 2 (continued)

Author, year	Study design	Total no. of patients	Evaluable: proton	Evaluable: non-proton	% Female	Tumour type	% CSI	Dose (Gy)	Age at treatment/ baseline testing/ diagnosis	Time from treatment to neurocognitive evaluation	Neurocognitive tests
											Lobe Executive test
Peterson, 2018	Retrospective	39	22	17	38.5	Glioma (4), medulloblastoma/PNET (16), germ cell (4), other (1)	Not mentioned	Not mentioned	At treatment photon-mean 9.1 ± 2.0, proton-mean 10.0 ± 2.3	Mean 2.35 ± 1.38	WISC 4th ed.
Pulsifer, 2018	Retrospective	155	114	0	51.6	Glioma (22), medulloblastoma/PNET (54), ependymoma (25), germ cell (12), craniopharyngioma (28), other (14)	38.7	CSI: 23.4 (18.0–36.0), CSI-total: 54.0 (30.6–54.0), focal: 52.2 (30.6–57.6 Gy)	At baseline testing mean: 8.9 ± 5.1	Mean: 3.6 ± 2.4	BSID 2nd ed., WISC 4th ed., WPPSI – 3rd ed., WAIS 3rd/4th ed.
Roth, 2020	Retrospective	70	70	0		Glioma (15), medulloblastoma/PNET (28), ependymoma (8), germ cell (10), craniopharyngioma (5), other (4)	53	CSI: 54 (45–55.8), focal: 50.4 (45–60)	At treatment: CSI (mean 7.8 ± 3.93, focal (mean 7.04 ± 4.24)	CSI (mean 5.2 ± 2.76), focal (mean 5.63 ± 2.49)	WISC
Yock, 2016	Prospective	59	59	0	44	Medulloblastoma (59)	100	CSI: 23·4 (IQR 23·4–27·0), boost: 54·0 (IQR 54·0–54·0)	At treatment: 6.6 (IQR 5.1–9.9)	7 (IQR 5.2–8.6)	WISC
Zureick et al.	Retrospective	70	70	0	51.4	Glioma (12), medulloblastoma/PNET (31), ependymoma (6)	50	Not detailed	At treatment − 12.1 (5.0–22.5)	3.0 (1.1–11.4)	CMS, WMS 3rd ed., WISC 4th ed., WPPSI 3rd ed., WAIS 4th ed.

Dose and length in median (range) unless otherwise mentioned

Lower number of evaluable patients due to the absence of neurocognitive assessment

BSID Bayley Scales of Infant Development, *CMS* Children's Memory Scale, *CPT* Conners' Continuous Performance Test-II, *CSI* Craniospinal irradiation, *D-KEFS* Delis-Kaplan Executive Function System, *LIPS* Leiter International Performance Scale, *MDI* Mental Development Index, *SBI* Stanford-Binet Intelligence Test, *VMI* Beery-Buktenica Developmental Test of Visual-Motor Integration, *WASI* Wechsler Abbreviated Scale of Intelligence, *WIAT* Wechsler Individual Achievement Test, *WISC* Wechsler Intelligence Scale for Children, *WJA* Woodcock-Johnson Tests of Achievement, *WJCA* Woodcock-Johnson Tests of Cognitive Abilities, *WMS* Wechsler Memory Scale, *WPPSI* Wechsler Preschool and Primary Scale of Intelligence, *WRAML* Wide Range Assessment of Memory and Learning, *WSI* Wechsler Scale of Intelligence

with proton. The number, however, is likely to be an overestimation due to probable overlap of patients reported by the same centres with researchers from Massachusetts General Hospital and Texas Children's Hospital produced five and three reports, respectively. Other centres reported one report each and one is a combined analysis from two centres including Texas Children's Hospital. Due to the potential lack of independence, we refrained from summing the number of patients in the preceding subsections and the number of reports were included instead. The sample size ranged between 12 and 144. Median/mean time to evaluation was more than 2 years for all included reports. Tumour types are diverse and generally mirror the prevalence of diagnoses treated with radiotherapy. No study reported an extraordinary prescription dose.

Studies comparing proton therapy and photon radiotherapy outcomes

Four studies presented a comparison between proton therapy and proton radiotherapy in terms of cognitive functioning (Table 3) [25, 27, 31, 35]. Three of the studies (Kahalley et al. 2016, Gross et al. 2019 and Kahalley et al. 2020) reported a complete treatment account of these patients including the dose and treatment type while Peterson and Katzenstein (2018) did not provide details of the treatment given. Kahalley et al. (2020) accrued patients treated for medulloblastoma with CSI while others accrued patients treated with either focal or CSI for diverse diagnosis [25, 27, 31, 35].

Overall, in all cognitive measures where the differences were significant, patients treated with proton therapy performed better. General cognition was found to be better among patients treated with proton therapy in three reports including in a cohort of patients treated with CSI [27, 31, 35]. For working memory, both Gross et al. and Kahalley et al. found better outcomes for proton therapy. Across time, the slopes of changes for working memory are significantly different, stable for proton and decline for photon [35]. For patients treated with CSI, Kahalley et al. found a significant decline in processing speed in both proton and photon groups. While in a cohort of diverse diagnosis, patients treated with proton performed better with CSI found to be a significant predictor for worse outcomes [27]. For verbal reasoning, Gross et al. found a significant difference between proton and photon groups while Kahalley et al. (2020) found neither significant difference nor significant slope of change [27, 35]. Other measures where proton groups were found to perform better include visual-motor, reading/decoding, written calculation and perceptual reasoning [27, 35].

Factors affecting cognition were diverse with hydrocephalus requiring shunt and CSI were consistently associated with poorer cognitive outcomes.

Association between PT and general cognition (eight reports)

Eight reports determined the change to general cognition, the majority of which using the Wechsler Intelligence Scale for Children (WISC) instrument [24–26, 28, 30, 33, 36, 37]. Two reports on patients receiving focal therapy found no significant difference while in combined cohorts, CSI patients performed worse than either baseline or normative mean (Table 4). The only report on CSI alone found significant mean change per year. Significant factors impacting general cognition for proton therapy include CSI, dose, posterior fossa syndrome and follow-up.

Association between PT and verbal IQ (six reports)

Weschler verbal IQ tool was the most utilised instrument for verbal IQ. Three reports are from the same institution [24, 26, 34] and another three from another institution [30, 32, 38]. In verbal IQ, CSI was found to be an important predictor of poorer outcomes [32, 34, 38].

Association between PT and perceptual reasoning (five reports)

In five reports reporting the changes of perceptual reasoning [24, 26, 30, 34, 38], Roth et al. and Pulsifer et al. found a significant difference to normative mean and between age and treatment groups [24, 38]. Only the CSI group was implicated in Roth et al., while the perceptual reasoning among patients treated with focal therapy was not statistically different to normative mean [38]. Pulsifer et al. found no sustained impact in post hoc analyses between focal and CSI group [24]. In contrast, York et al. found no significant mean change of perceptual reasoning score per year despite accruing only CSI patients [34].

Association between PT and working memory (four reports)

In four reports on working memory, significant changes were associated with CSI in two reports [24, 38] which were in contrast to Yock et al. found no significant mean change per year for a cohort of patients treated with CSI. Peterson et al. reported a significant decline but the impact of CSI cannot be verified.

Association between PT and processing speed (five reports)

In five reports on processing speed, CSI was a significant factor for significant cognitive decline. Roth et al. found a

Table 3 Comparison between cognitive outcome following paediatric proton and photon therapy for brain tumours

First author, year	Main cognitive measure	Main outcome	Significant predictors for worse cognitive outcome
General cognition			
Gross, 2019	FSIQ (Wechsler)	Higher FSIQ for proton	Hydrocephalus requiring shunt
Kahalley, 2016	FSIQ (Wechsler)	Worse IQ change for photon. IQ slopes did not differ between groups	IQ test type—Leiter scores, worse performance scores, lower SES
Kahalley, 2020	FSIQ (Wechsler)	Worse IQ slope for photon therapy, stable slope for proton	
Working memory			
Gross, 2019	Digit span	Proton significantly better	Younger
Kahalley 2020	WMI (Wechsler)	Worse slope for photon therapy, stable slope for proton	-
Peterson, 2018	WMI (Wechsler)	Not significant	-
Processing speed			
Gross, 2019	PSI (Wechsler)	Proton significantly better	CSI, posterior fossa syndrome
Kahalley, 2020	PSI (Wechsler)	Significant decline for proton and photon	
Peterson, 2018	PSI (Wechsler)	Not significant	-
Verbal reasoning			
Gross, 2019	VCI (Wechsler)	Proton significantly better	Younger, lower SES
Kahalley, 2020	VCI (Wechsler)	Not significant	-
Perceptual reasoning			
Gross, 2019	PRI (Wechsler)	Nonverbal reasoning—not significant	Lower SES, hydrocephalus requiring shunt and CSI
Kahalley 2020	PRI (Wechsler)	Perceptual reasoning—higher mean scores for proton, significant difference of slopes between proton and photon	-
Other measures			
Gross, 2019	Delayed story memory task (WRAML2 or CMS)	Memory—not significant	Lower SES, black, hydrocephalus requiring shunt
	Visuographic skills (VMI)	Visual-motor integration—proton significantly better	CSI, longer time to evaluation
	Reading/decoding (WIAT or WJA)	Academic skills—proton significantly better	None
	Written calculation (WIAT or WJA)	Academic skills—proton significantly better	Higher SES, hydrocephalus requiring shunt and CSI

FSIQ full-scale intelligence quotient, *WMI* working memory index, *PSI* processing speed index, *VCI* verbal comprehension index, *PRI* perceptual reasoning index, *SES* socioeconomic status, *CSI* craniospinal irradiation, *VMI* Beery-Buktenica Developmental Test of Visual-Motor Integration, *WRAML* Wide Range Assessment of Memory and Learning, *CMS* Children's Memory Scale, *WIAT* Wechsler Individual Achievement Test, *WJA* Woodcock-Johnson Tests of Achievement

significant change to normative mean for patients treated with either focal therapy or CSI.

Association between PT and memory (two reports), executive function (two reports) and motor (one report)

Two reports highlighted the change to memory using delayed story memory task, Rey-Kim memory task or Weschler Memory Scale [27–29]. Compared with baseline, Zureick et al. found a significant and a trend toward significant change for immediate and delayed verbal memory, respectively. This is in concordance to the findings by Park et al. in comparison with normative means. Park et al. found no difference between the executive function outcome in a combined focal and CSI cohort. Antonini et al. who subjected patients to a battery of specialised executive function test (Delis–Kaplan Executive Function System) and separated between those treated with CSI and focal therapy observed differences between them. Patients treated with CSI performed worse than normative means in word reading score and more errors in inhibition/switching tasks in Colour-Word Interference test which assesses verbal inhibition. They also performed worse in number-letter switching and number and letter sequencing in

Table 4 Comparison between cognition following proton therapy to baseline, normative mean or radiotherapy-naïve paediatric brain tumour patients

First author, year	Treatment technique	Comparison	Main outcome	Significant predictors for worse cognitive outcome
General cognition				
Greenberger, 2014	Focal	Baseline	No significant difference	High-risk dose
Kahalley, 2019	Focal and CSI	Radiotherapy-naïve	Proton CSI significant decrease. Significant slope difference between CSI to both focal and surgery	Posterior fossa syndrome
Macdonald, 2013	Focal	Baseline	No significant difference	None
Park, 2017	Focal and CSI	Normative mean	No significant difference	None
Pulsifer, 2018	Focal and CSI	Baseline	significantly worse than baseline	Longer follow-up interval, younger, higher baseline score, CSI
Roth, 2020	Focal and CSI	Normative	CSI worse than normative mean. No significant difference for focal	Not studied
Yock, 2016	CSI	Baseline	Significant mean change per year	Younger, involved field
Zureick, 2018	Focal and CSI	Baseline	No significant difference	Not studied
Verbal IQ and language skills				
Antonini, 2017	Focal and CSI	Normative	CSI: Worse letter fluency Focal: No difference	Older age at testing and RT
Greenberger, 2014	Focal	Baseline	No significant difference	Younger, high-risk dose
Kahalley, 2019	Focal and CSI	Radiotherapy-naïve	No significant change and slope difference for both CSI and proton	Posterior fossa syndrome
Park, 2017	Focal and CSI	Normative	No significant difference	None
Pulsifer, 2018	Focal and CSI	Between age and treatment group	No significant difference	None
Roth, 2020	Focal and CSI	Normative	CSI worse than normative mean, focal no difference	Not studied
Yock, 2016	CSI	Baseline	Highly significant mean change per year	None
Perceptual reasoning				
Greenberger, 2014	Focal	Baseline	No significant difference	None
Kahalley, 2019	Focal and CSI	Radiotherapy-naïve	No significant change and slope difference	Posterior fossa syndrome, history of VP shunt,
Park, 2017	Focal and CSI	Normative mean	No significant difference	None
Pulsifer, 2018	Focal and CSI	Between age and treatment group	Significant	None in post-hoc
Roth, 2020	Focal and CSI	Normative mean	CSI worse than normative mean, focal no difference	Not studied
Yock, 2016	CSI	Baseline	No significant mean change per year	None
Working memory				
Kahalley, 2019	Focal and CSI	Radiotherapy-naïve	Proton CSI significant decrease. No slope difference between CSI to both focal and surgery	Posterior fossa syndrome
Peterson, 2018	Not mentioned	Baseline	Significantly worse than baseline	Age, gender (direction not mentioned)
Pulsifer, 2018	Focal and CSI	Between age and treatment group	Significant	CSI
Roth, 2020	Focal and CSI	Normative	CSI worse than normative mean, focal no difference	Not studied
Yock, 2016	CSI	Baseline	No significant mean change per year	None
Processing speed				
Kahalley, 2019	Focal and CSI	Radiotherapy-naïve	Proton CSI significant decrease. Significant slope difference between CSI to both focal a nd surgery	Posterior fossa syndrome, history of VP shunt
Park, 2017	Focal and CSI	Normative	No significant difference	None

Table 4 (continued)

First author, year	Treatment technique	Comparison	Main outcome	Significant predictors for worse cognitive outcome
Peterson, 2018	Not mentioned	Baseline	Significantly worse than baseline	None
Pulsifer, 2018	Focal and CSI	Between age and treatment group	Significant	CSI
Roth, 2020	Focal and CSI	Normative	CSI and focal worse than normative mean	Not studied
Yock, 2016	CSI	Baseline	Highly significant mean change per year	None
Memory				
Park, 2017	Focal and CSI	Normative	Significantly worse than population mean	None
Zureick, 2018	Focal and CSI	Baseline	Significantly lower than baseline for delayed verbal memory	Higher dosimetric index, lower baseline score and female
Executive functions				
Antonini, 2017	Focal and CSI	Normative	Conners' Continuous Performance Test CSI and focal: no difference	History of craniotomy, higher total RT dose, younger age
			Colour word interference CSI: Lower processing word reading score and more errors in inhibition/switching task Focal: No difference	Infratentorial tumours
			Trail making test CSI: Worse Number-Letter Switching, Number sequencing and Letter sequencing tests Focal: better Number-Letter switching errors	Female, history of a shunt
Park, 2017	Focal and CSI	Normative	No significant difference	None
Motor				
Antonini, 2017	Focal and CSI	Normative	CSI: Worse motor coordination and visual perception Focal: Worse motor coordination	Female, history of a shunt, supratentorial

the Trail Making Test which assesses the flexibility of thinking [39]. Patients treated with focal therapy were not significantly different to normative mean and in one instance performed better than normative means.

Effect of dose factors

Three reports found significant associations between dose factors and cognition (Table 5). Only Antonini et al. who analysed the effect of total dose found a significant association to cognition while others found no such association or used the dose measure to adjust for multivariate analysis [29–31, 34, 38]. Two studies performed dose analyses of specific structures (temporal lobe and hippocampus) and found significant association overall cognition, verbal comprehension and verbal and visual memory [26, 28].

Discussion

We conducted the first systematic review to methodically accumulate and synthesise the evidence of cognitive changes

Table 5 Effects of dose measures to cognition

First author, year	Dose measure	Effect to cognition
Antonini, 2017	Total dose	Slower responding
Greenberger, 2014	Dose distribution to left temporal lobe/hippocampus	Overall cognition and verbal comprehension
Zureick, 2018	Dose distribution to left hippocampus	Verbal and visual memory scores

following proton therapy among paediatric brain tumour patients. Based on this systematic review, we found that while the cognitive decline is evident, they were not profound for focal therapy at about a median of 2- to 3-year follow-up following proton therapy of paediatric tumours. Significant changes impacted a segment of patients, i.e. those treated with craniospinal irradiation and those with hydrocephalus. Furthermore, available evidence suggests the reduction of cognitive decline for patients treated with proton compared with photon. Despite some evidence of the effect of dose distribution to cognition, reports focusing on the effect were limited to allow a definitive conclusion.

Initially, a meta-analysis was planned to provide estimates of cognitive changes by combining the information across studies. However, due to (1) variation of comparisons performed including to normative means, baseline and radiotherapy-naïve, (2) highly probable lack of independence of cohorts reported by the same groups and (3) hypothesis-generating nature of most studies, meta-analysis is not optimal. However, with the growing number of new centres offering proton therapy, these technical issues are likely to be resolved in the future and meta-analysis should then be performed. To date, only seven reports presented reasonably large cohorts (> 50) of patients treated with proton therapy. Similarly, we are optimistic to see reports with larger cohorts in the future.

The neurocognitive function for paediatric patients with intracranial tumours has some level of impairment at diagnosis related to age, location, posterior fossa syndrome and type of tumour [29, 35, 40]. This may have some implications in a significant number of studies which did not collect the baseline cognitive function and compared post-treatment measures with normative means [41]. While the comparisons with normative means may not be methodologically optimal, in many domains of neurocognition, patients treated with proton therapy were not significantly lower in cognitive measures than that of the normal population. This observation of the lack of significant difference to normative means gives a substantial assurance that the decline, if any, is not profound. However, comparison with normative means may not provide a clear picture for physicians and guardians on how the children may change following therapy which may impact educational and pharmacological intervention decisions [42]. For future studies, a proper baseline cognitive assessment to allow better quantification of the magnitude of change is recommended.

In the current climate of healthcare financing, there are growing needs for new technology, including proton therapy, to be proven to be cost-effective. While dosimetric studies have repeatedly shown the benefit of proton therapy, societal demands require the physical advantage of proton therapy to be translated to clinical benefit to the patients [43]. Direct comparison in a randomised controlled trial is yet to materialise, potentially never will, due to ethical concern of randomising a patient to a dosimetrically proven inferior treatment arm. Furthermore, other clinical benefits of PT have been observed including to reduce late endocrine abnormalities, radiogenic second cancers and cardiac mortality [44, 45]. In this review, we included four reports that have attempted to compare the outcome of proton therapy in comparison with photon therapy. All of which were from retrospective cohorts [25, 27, 31, 35]. Generally, studies found less impairment for patients treated with proton [27, 31]. Kahalley et al. noted that the IQ slopes did not differ between proton and photon groups despite the persistent difference between groups [31]. However, in a more recent work to compare intellectual trajectories between paediatric patients treated for medulloblastoma with comparable contemporary protocols, the slopes of change of proton and photon that were found to be different with proton showed stable performance over time since diagnosis while photon showed a statistically significant change per year [35]. Of note, the study by Kahalley et al. accrued cohorts of patients from two countries with different availability of proton therapy that may reduce biases associated with treatment selection due to differences in socioeconomic status, prognosis and tumour characteristics [35].

We categorised reports on cognitive changes based on the neurocognitive tests/domains with the assumption that they are not similarly affected by radiation therapy. Our results suggest that patients treated with CSI performed worse than those treated with focal therapy consistently across neurocognitive domains. For full-scale IQ, verbal IQ, perceptual reasoning, working memory and executive functions, results showed that either no significant change for focal proton therapy or, in combined cohorts of focal therapy and CSI, CSI was the risk factor for a significant decline. For processing speed, memory and motor, both focal and CSI groups were affected. This is an important observation in twofold; first, they are clinically relevant and second, future clinical studies should separate the groups to allow appropriate comparisons. It should be noted that since the whole brain is irradiated in CSI, the protective effect of proton therapy to cognition is likely to be small. However, the reduction of dose may be more apparent during tumour bed boosts. Efforts to reduce the volume and dose of radiation to normal brain tissue are again highlighted in these findings. There are other factors found to be significant predictors for worse outcomes. However, due to the lack of consistency across studies, they need further evaluations.

Four reports performed analyses of the cognitive changes across time and resulted in interesting observations. Kahalley et al. in 2016 reported that the slope of change between proton and photon therapy did not differ suggesting that patients treated with proton may have a similar trajectory to those treated with modern photon therapy [31]. In another report by Kahalley et al. in 2019, the trajectory of change for focal proton therapy and radiotherapy-naïve patients was not

significantly different suggesting a similar impact of local surgery to proton therapy to cognition [30]. Among patients treated with CSI, York et al. showed a significant slope of decline for general cognition [34]. In contrast, Kahalley et al. (2020) found the trajectory to be stable for patients treated with proton therapy for general cognition, working memory and perceptual reasoning. The analysis based on the trajectory of change is potentially superior compared with a single observation to show patterns of change as patients are subjected to periodical and long-term assessment and should be considered in future study design.

Only two studies performed analyses on the effects of dose to brain substructures to cognition. This is an interesting question to answer as there is significant evidence that certain areas of the brains are found to be correlated to cognitive decline among adult brain tumour survivors [46] and children treated with photon therapy [47–49] which can be a basis for treatment optimisation [50]. Future studies should be encouraged to assess the effect of dose distribution to cognition as the dose–volume response relationships will allow better individualisation of treatments. An international collaboration to analyse normal tissue radiation dose–volume response relationships for paediatric cancer patients has been established and the reports from the collaboration are eagerly awaited [51].

We should note some limitations of the systematic review. First, the length of time from treatment to neurocognitive evaluation was diverse which may impact the result of comparisons. However, mean/median times from treatment to neurocognitive evaluation were more than 2 years for all reports. Second, there were other confounders which may affect neurocognitive performance not taken into consideration. For example, as most patients received chemotherapy as part of the treatment, the effect of cognitive changes due to cisplatin-related hearing loss was indifferentiable to changes associated with radiation. Third, it is acknowledged that selection bias where negative studies are less likely to be published and thus not be searchable may influence the observation.

Conclusion

Studies showed that the strong effects of treatment type with craniospinal irradiation consistently caused a more significant decline in cognition compared with focal therapy. The clinical neurocognitive evidence of the superiority of proton over modern photon therapy is evident and further investigations to remove biases may be necessary potentially through analyses of multi-institutional cohorts. Long-term longitudinal assessment is recommended. The effect of dose distribution to cognitive changes is in general still poorly studied.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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