Neuroprotective benefits of proton beam therapy for paediatric central nervous system tumours: a review of evidence

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BACKGROUND

Proton beam therapy (PBT) is often used for paediatric central nervous system (CNS) tumours for its potential to reduce neurocognitive effects. This is due to the dosimetric properties of PBT, providing a more conformal dose to the target volume and lower integral dose to healthy tissue compared with photon therapy[1]. Overall helping lower dose to critical structures in the brain, reducing long-term neurocognitive deficits and potentially improving quality of life (QOL).

The most common tumour types identified were craniopharyngioma, ependymoma, intracranial germ cell tumour, low- and intermediate-grade gliomas and medulloblastoma. Example low-grade glioma protocol doses for The Christie can be seen below.

Low-grade glioma	Dose delivered, Christie, Manchester
Optic pathway	- Usually 50.4Gy (RBE) in 28 fractions - Selected cases may be up to 52.5Gy-54Gy (RBE) in 29-30 fractions
Brainstem	- 50.4Gy (RBE) in 28 fractions - 52.2 – 54Gy (RBE) in 29-30 fractions to meet OAR targets
Pleomorphic Xanthoastrocytoma(PXA, WHO grade II)	- 54Gy (RBE) in 30 fractions
Other cases	- 54Gy (RBE) in 30 fractions as standard

AIMS

- To identify and critically appraise current literature relating to the neurocognitive late effects of CNS paediatric cancer diagnosis, and the neuroprotective benefits of proton beam therapy.
- To critically evaluate current evidence regarding the benefits of proton beam therapy in reducing neurocognitive effects more than two years following treatment.

METHOD

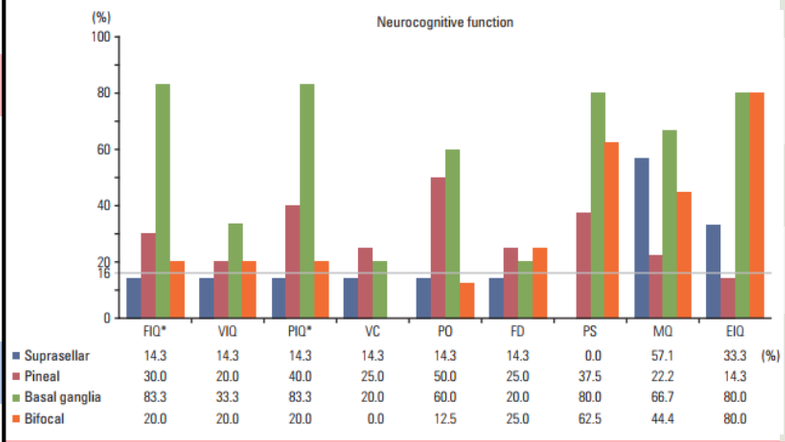
PubMed and Scopus were systematically searched to identify appropriate studies on neurocognitive late effects following PBT according to PRISMA protocols[2]. Key words were chosen based on PICO criteria[3] with main themes including PBT, paediatric CNS tumours and neurocognitive tests, inclusion and exclusion criteria are below.

Inclusion criteria	Exclusion criteria
Paediatric CNS tumours, PBT, neurocognitive deficits	Photon therapy, <2002

RESULTS

Ten papers were selected and appraised (mean no. of patients(range): 63.1 (18 -114)). All reports included PBT only, with seven including Craniospinal Irradiation (CSI). One exception for photon contingency treatment was accepted. Over half of the studies included baseline assessments. There were multiple measures used for neurocognitive effects seen at baseline and as part of follow-up. In general, Full Scale Intelligence Quotient (FSIQ) was not observed to differ significantly from the normative population. An example of tests used and differences shown can be seen in the table on the right. Deficits at follow-up were often predicted at baseline showing the diagnosis alone could be indicative of poor neurocognitive function[5].

Significantly poorer outcomes were observed following CSI treatment, compared with focal treatment where minor cognitive changes were identified in characteristics such as processing speed and working memory index. Tumour location was identified as a predictor for poor neurological status, with basal ganglia germ cell tumours demonstrating the most deficit compared to other locations shown in the figure below[8].



Author	Neurocognitive tests	Outcomes
Antonini[4]	CPT-II, D-KEFS	Focal – no SD CSI – SD in multiple domains
Fournier-Goodnight[5]	WIS, CPT-II, WMI, D-KEFS, BASC-2,	Baseline testing only
Heitzer[6]	WIS	No SD
Jimenez[7]	WIS,	No SD
Park[8]	Korean-WISC, Korean-WAIS, Rey-Kin memory test	Focal - SD dependant on tumour location CSI - SD
Pulsifer[9]	WISC-IV, WAIS-III	SD in processing speed CSI - SD
Pulsifer[10]	BSID 2nd ed, WISC 4th ed, WPPSI 3rd ed, WAIS	SD in younger patients and CSI
Roth[11]	WISC	Focal – some SD CSI – SD in changes per year
Yock[12]	FSIQ and its domains	SD in delayed verbal memory
Zureick[13]	CMS, WMS-III	SD when increased hippocampi dose

KEY: SD = significant differences, CPT-II = Connors' continuous performance test, D-KEFS = Delis-Kaplan executive function system, WIS = Wechsler intelligence scale, WMI = Working memory index, BASC = Behaviour assessment system for children, BSID = Bayley mental development index.

CONCLUSION

Evidence continues to indicate cognitive sparing years after treatment, due to beneficial dosimetric properties of PBT. Patients receiving focal treatment demonstrated a consistently lower risk of cognitive deficits compared to CSI patients; indicating a requirement for separate research directives. Reduced dose to certain cranial structures may be a protector of long-term neurocognitive deficit. Longer-term follow up is required to determine if cognitive risk continues to stay within the limits of the normative population or decreases over time. Neuroprotective benefits of PBT were seen across much of the data, indicating PBT continues to spare cognitive function over time.

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