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Recommendations for Assessing Cognitive Risks in Young Children Treated for Ependymoma for Clinical and Research Protocols: Evidence from a Systematic Literature Review

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Abstract: *Background*: Current treatment approaches for pediatric ependymoma differ between North American and European studies. Post-surgical adjuvant irradiation is used in children aged <36 months in North America, whilst European approaches use chemotherapy to avoid or defer radiotherapy until three years of age, in order to avoid late neurocognitive toxicity. To establish evidence for the effects of cranial radiotherapy in children aged <36 months with ependymoma on neurocognitive outcomes, we conducted a systematic literature review assessing methodological approaches for measuring neurocognitive outcome. *Methods*: Eight databases were selected to perform an advanced search, retrieval and systematic review of papers describing neurocognitive outcome in children diagnosed with ependymoma who received cranial radiotherapy at <36 months. *Results*: Limitations of published data permitted descriptive analysis only. Considerable variation in reporting survival rates, techniques and timing of psychometric testing and the results of neurocognitive outcomes was identified. *Conclusions*: The review identified significant inconsistencies of neurocognitive testing, particularly literacy skills, developmental time points for testing and methods of data reporting. The role of the cerebellum for cognitive development, especially reading, has been inadequately evaluated in published studies. Recommendations are made to improve assessment methods, and time points for testing, so that reports do not fail to identify children who acquire deficits as they mature through childhood and adolescence. We conclude that claims that radiation treatment for ependymoma administered aged <36 months is associated with limited neurocognitive consequences, are not supported by the literature.

Keywords: Paediatric, ependymoma, cognitive, risk, outcome.

INTRODUCTION

Ependymoma arising at less than 16 years of age account for 10% of brain tumours in the age group, >50% present in the pre-school age group (<5yrs) and <80% presenting by eight years of age [1,2]. Ninety percent of pediatric ependymomas are intracranial in origin with two-thirds arising from the lining of the fourth ventricle in the posterior fossa [3]. The young age bias coupled with the complexities of achieving complete resection of tumour involving the brain stem and cerebellum have contributed to poor outcomes because of incomplete resections and restricted use of radiotherapy linked to risks of neurotoxicity affecting cognitive development and other long-term clinical sequelae [4-6].

Concerns regarding the long-term cognitive and learning impairments of irradiating immature brain structures, particularly supratentorial regions and its impact on developing cognitive functions, have led some centres to employ strategies to delay or avoid the delivery of radiotherapy by using chemotherapy first. Understandably, much research in neurooncology focuses on survival rates as primary outcome measures, whilst lower priorities have historically been allocated to neurocognitive and learning outcome measures as drivers for change in treatments [7]. An exception to this [8] is the reporting from North America of the use of highly conformal radiotherapy as the primary adjuvant therapy in children aged <36 months with ependymoma [9]. This approach contrasts with many European centres which are continuing to use radiotherapy-deferral strategies with adjuvant chemotherapy.

This difference in clinical practice highlights the importance of considering the neurocognitive consequences for radiotherapy given to the very immature brain, particularly the posterior fossa [10]. Although the cerebellum has been thought to be devoted almost entirely to motor control [11], namely skilled voluntary movements, muscle tone, posture and gait, a growing body of empirical data implicates the developing

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cerebellum in diverse higher cognitive functions [12], especially acquisition of literacy skills [13-15]. Furthermore, neuroendocrine sequelae and second cancers after radiotherapy, adversely influence quality of survival [16-18]. In order to investigate the impact of different treatment regimes [19] a systematic literature review of publications describing the neurocognitive outcomes of children with ependymoma who received radiotherapy at <36 months of age was conducted.

MATERIALS AND METHODS

Search Strategy

An advanced search was performed in AMED, BIOSIS Previews, CAB Abstracts, EMBASE, Ovid MEDLINE, PsycINFO, CINAHL and Cochrane Library for articles published in English from database commencement to date. All databases were searched using the terms: ((ependymoma*) OR (post* adj2 fossa*) OR (post*-fossa*)) AND ((child*) OR (p?ediat*)) AND ((radiotherapy*) OR (radiat* adj2 therap*) OR (irradiat*) OR (stereotactic adj2 surger*) OR (gamma adj2 knife) OR (IMRT) OR (chemotherap* adj2 wafer*) OR (proton adj2 therap*) OR (photon adj2 therap*) OR (brachytherap*)) AND ((neurocognit*) OR (neuro adj2 cognit*) OR (psychometric*) OR (neurometric*) OR (learning*) OR (educat*) OR (neuropsych*) OR (psycholog*) OR (cognit*)).

Selection Criteria

Three members of the review team read the retrieved papers independently and identified data for the agreed categories presented in Tables **1**, **2** and **3**. Inclusion was dependent on two criteria:

1. The paper reported participants receiving irradiation at three years of age or under for the treatment of ependymoma.

2. The paper reported participants' neurocognitive or psychometric outcomes.

Level of evidence was determined independently by three investigators using indicators as defined by the Centre for Evidence Based Medicine [20] (Table **1**).

Statistical Analysis

The retrieved data did not permit meta-analysis or use of a vote count procedure because of inconsistencies across studies in their use of comparable neuropsychological and psychometric assessments or lack of detailed reporting of children with significantly impaired performance. Consequently, a descriptive analysis was performed. Data were presented using the following categories: number of patients with ependymoma; age at irradiation; grade and site; non-radiological treatments received; residual disease stated; presence of hydrocephalus; radiation dose; survival rate; psychometry used; described impairment; global outcomes and level of evidence [20].

Table 1: Oxford Centre for Evidence-Based Medicine Levels of Evidence Summary

Levels of Evidence	Requirement
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none case series
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study
2c	'Outcomes' research
3a	Systematic review (with homogeneity) of case control studies
3b	Individual case-control study
4	Case series
5	Expert opinion without critical appraisal

RESULTS

In total, 291 papers were retrieved. Figure **1** illustrates the retrieval process which was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21].

After removing duplicates, the remaining 141 papers were evaluated to determine inclusion. Nine studies met the inclusion criteria (Table **2**). A further five studies did not provide specific information for age at the time of irradiation but stated that patients were less than five years (Table **3**). An additional 11 studies indicated the inclusion of patients with ependymoma but age could not be determined from data provided (Supplementary Table).

Retrieved Studies of Children <36 Months Diagnosed with Ependymoma

Nine references were retrieved from 1990-2011 (Table **1**). Of the retrieved references, 88.8% (8/9 papers) met level 2c [20] for quality of evidence with

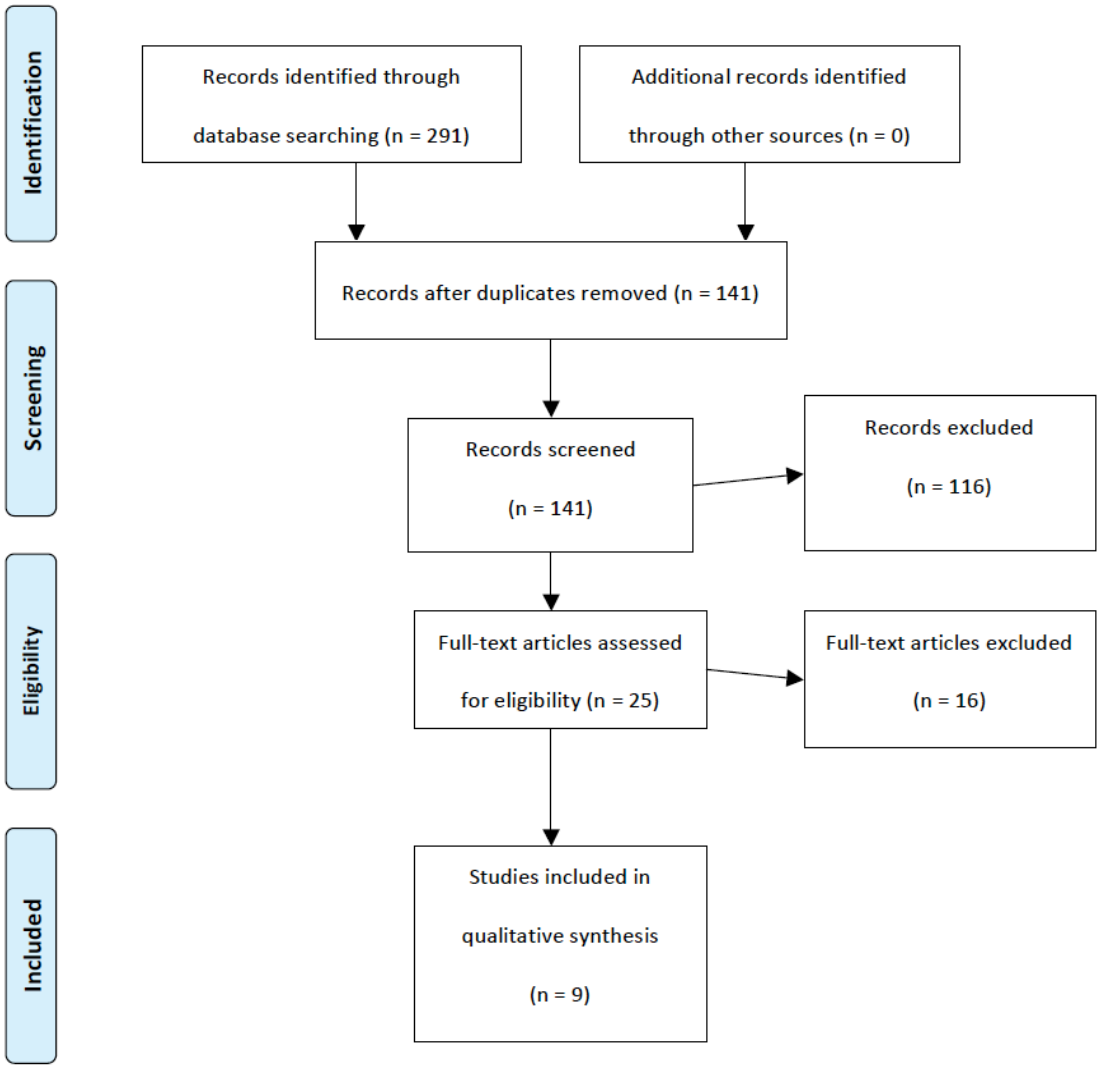

Figure 1: Retrieval Algorithm in accordance with PRISMA Guidelines.

[25] at 3b [20]. Two pairs of papers described the same patients [8, 22, 24, 27]. The total number of patients involved in all nine studies was 184. Of these, 35.9% (66/184) were irradiated at <36 months (0.67 [8 months]-2 years). The first study [7] contained two protocols for irradiation where the highest dose was 70.4Gy prior to 2001 and then 59.4Gy from 2001 onwards. Mean and standard deviation for all ages were not calculated as three papers [8, 26, 27] did not specify a mean but stated patients were irradiated at <36 months. Of the 35.9% irradiated at <36 months, 80.3% (53/66) had an infratentorial location with 13.6% (9/66) having supratentorial. The remaining four patients (6.5%) irradiated at <36 months from one paper [23] were not identified as either infra- or supratentorial.

Of the 66 patients, all received neurosurgery. For 13.6% (9/66) the level of resection was unspecified, 86.4% (57/66) had Gross-Total Resection (GTR), 6.1% (4/66) had Near-Total Resection (NTR) and 9.1% (6/66) had Subtotal Resection (STR). Of all patients, 25.8% (17/66) received chemotherapy in addition to irradiation. A maximum of seven patients may have received chemotherapy in addition to irradiation but this is not described [7, 25]. Where reported, hydro-cephalus was present in 74.2% (49/66) of patients irradiated at <36 months.

Radiation and Chemotherapy Treatment Received

Radiation dosage was reported in 77.7% (7/9) of the studies, ranging from 40-70·4Gy. For [7] in the 1994-2001 period, patients with complete tumour excision received hyperfractionated RT (1.1. Gy twice a day) to the tumour bed plus 1-2 cm margins up to a total dose of 70.4 Gy. Where residual tumour was identified, four chemotherapy (CT) doses with vincristine, etoposide

Table 2: Retrieved Studies of Children <36 Months Diagnosed with Ependymoma

Refs.	No of Pts with EPD	Age at Irradiation	Grade & Site	Non radiological treatments		Residual Disease	Hydro-cephalus	Interven-tion (radiation dose)	Survival rate	Psychometric Tests	Impairment	Core Outcomes	Level of Evi-dence
				Surgery	Chemo-therapy								
Poggi, *et al.* (2011) [7]	All 23 pts had EPD, 4/23 (17%) were irradiated under 3yrs	<3 years at irradiation: Pt 1: 29 months Pt 3: 20 months Pt 4: 14 months Pt 5: 22 months Of all 23 pts: Mean = 6.09 yrs (SD: 3.89)	Of 4 <3: 1 supratentorial 3 subtentorial Of all 23 pts: 17 infratentorial 6 supratentorial.	Of all 23 pts: Surgery in 18 pts (gross-total in 16 pts)	Of all 23 pts: Chemo-therapy n=12.	When residual disease was present, regardless of the tumour grade, VEC chemotherapy was prescribed prior to RT with the option of second surgery prior to irradiation. Numbers of pts with residual disease not stated.	Of all 23 pts: Present in 26.1% (n=6)	59.4-70.4 Gy	Not stated	• 1 pt < 3yrs underwent neuropsychological evaluation - attention and they were evaluated over time by age-appropriate tests. (others deemed too young but all has psychosocial skills measured) • WPPSI-R • Child Behavior Checklist • Vineland Adaptive Behaviour Scales-Expanded Form (VABS)	Pt 1: Cognitive deterioration over time, no attention problem s and they also had psychosocial problems Pt 3: Had psychosocial problems Pt 4 and 5: No psychosocial problems	• Pts >5 yrs had a lower mean IQ than pts <5yrs, though the difference was not statistically significant. • At neuropsychological levels, the mean scores of the whole sample are within the norm. • State that younger pts treated with RT did not appear to have cognitive impairment, but sample size v small. • 4 children did not undergo neuropsychological evaluation as they were too young for tests, and due to pre-school age no info on cognitive functioning in ecological setting available. Suggest that tumour location and preoperative or perioperative damage seem to affect the cognitive outcome to a greater extent than age at RT.	2c
Davis, *et al.* (2011) [22]	2/15 Same participants as Davis *et al.* 2009	Only 1 EPD pt received RT at 29 months	Not stated but see study below	Both EPD pts received surgery but level of surgery not described but see Davis *et al.* 2009 below	Both pts underwent chemother apy but exact regimen are not listed	Not stated	None present in pt who received RT Severe hydroceph alus reported pre-operatively in other pt, but then no post-operative recording	'Involved field radiother apy' but no mention of dose	Not stated	• WISC-IV (EPs would not have received this if under <6) • WPSSI-III (if look at appendix as it was clear that both EPs were <6 and it said children <6 received WPPSI) • WIAT-II • TEA-Ch • KABC-II • BOT-2	Pt 1 all scores on WPPSI III, WIAT II and BOT-2 were 2 or more SDs below mean as well as 2/5 In TEA-Ch, 4 items of KABC -II One key finding form the reading composite on the WIAT II for pt 1 was that their score was 47 (<2 SD below the mean) Pt 2 sig effect on all items of WPPSI III (except Processing	• Substantial intra- and inter-individual variation • Look at effect of hydrocephalus on all psychometric results - • Severity of hydrocephalus nor shunt placement were strong predictor s of neuro-developmental outcomes As participant 1 who had no hydrocephalus scored worse than participant 2 who had hydrocephalous • It is to be noted that participant 1 received radiotherapy at 29 months whereas participant 2 received surgery and chemotherapy aged 42 months only	2c

Table 2 Continued

Refs.	No of Pts with EPD	Age at Irradiation	Grade & Site	Non radiological treatments		Residual Disease	Hydro-cephalus	Interven-tion (radiation dose)	Survival rate	Psychometric Tests	Impairment	Core Outcomes	Level of Evi-dence
				Surgery	Chemo-therapy								
											Speed & Perceptual reasoning), all WIAT-II indices were borderline, 2/5 indices of TEA-Ch, 2/6 indices of KABC-II and 2/5 indices of BOT-II were 2 or more SDs below mean. Overall (7/25 completed subtests were 2SDs or more below). One key finding form the WIAT II Reading composite was their score of 74 (borderline)	Both ependymoma Pts had FSIQs 2 or more SDs below norm mean. More notably both had poor reading scores with one been more than 2 SDs below the mean and one having borderline reading scores	
Massimino, *et al.* (2011) [23]	All 41 pts had EPD 12/13 survivors were then followed up in study, 7 of whom received RT	1.11y, 2.01y, 2.01y 2.03y, 3.03y, 3.11y, 4.04y. 4/7 of these were <36months at irradiation	Of 41 original Pts Infratentorial (n=37[Cerebellum]) Supratentorial (n=4)	22/41 Complete Resection	All 41 Pts received one of two regimens (Regimen I- Vincristine, high-dose Methotrexate, plus Cyclophosphamide alternated with Cisplatin plus Etoposide; Regimen II - Vincristine plus Etoposide and Cyclophosphamide	19/41 showed residual disease Following repeat surgery 8 had residual disease	Present in 9/12 survivors followed-up	Up to 70.4 Gy if treated before 2001, conformal RT using conven-tional fractionation of 1.8 Gy a day up to a total dose of 54–59.4 Gy after 2001.	Event-free survival 3yrs - 26%, 5yrs - 26% 8 yrs - 23% Progression -free 27% at 3, 5 & 8 yrs Overall survival 3yrs - 48%, 5yrs - 37%, 8yrs - 28%	• Some IQ data reported, scholastic outcomes	Out of the 3 pts who did not receive any radiotherapy 1 had an IQ <2 SDs below mean. 1 had high average IQ and one was not explicitly reported, For the 4 pts who received radiotherapy <36 months: 2 had no IQ explicitly stated but were said to have 'normal behaviour and school outcomes';1 had a low average IQ and had attention and memory problems and 1 had difficulties with	• ' No better neurocognitive outcome was demonstrated in the few survivors who never received RT' ** V small sample size and IQ/scholastic outcome reporting is vague. No explanation of how the IQ scores were reached **	2c

Table 2 Continued

Refs.	No of Pts with EPD	Age at Irradiation	Grade & Site	Non radiological treatments		Residual Disease	Hydro-cephalus	Interven-tion (radiation dose)	Survival rate	Psychometric Tests	Impairment	Core Outcomes	Level of Evi-dence
				Surgery	Chemo-therapy								
											concentration, learning no IQ score was explicitly stated Of the three who had radiotherapy <5: 2 had IQs more than 2SDs below mean and 1 had a normal IQ		
Davis, *et al.* (2009) [24]	2/15	Only 1 EPD pt received RT at 29 months?	Pt who had RT - Inferior vermis/RH - Infratentorial Pt who didn't have RT: 4th ventricle - Supratentorial	1 = Near Total Resection Other = Macro-scopic Resection	Both pts underwent chemothera py but exact regimen are not listed	Not stated	None present in pt no. 1 Severe hydrocephal us reported pre-operatively in other pt	No RT identified.	Not stated	• KABC-II • BOT-2	Pt 1 -2SDs below the mean for Short-Term Memory, Visual Processing, Fluid Reasoning and Fluid Crystallised Index but average for Crystallised Ability for the KABC-II assessment and below 2 SDs from the mean for all items on BOT-2, Pt 2 no impairment shown on KABC-II, -2 SD below mean for Manual Coordination and Total Motor Composite on Bot-2	• Poorer performance for cerebellar pts across cognitive and motor domains - but considerable individual variation • It was noted that pts with vermis involvement like pt 1 who was irradiated here performed significantly lower on visual processing • Also noted that the 2nd pt who had EPD at 4th ventricle had suggested motor difficulties • 7/15 children sig impaired on at least one of five cognitive indices • Significant effect of tumour type/treatment found for overall measure of cognitive and motor ability	2c
Gerber, *et al.* (2008) [25]	1 2nd EPD p who was irradiated was irradiated >36 months (at 3.4yrs)	1.6 years & 3.4 yrs	Supratentorial (n=1) Anaplastic (n=1) It says the one at 3.4 is anaplastic infratentorial and 2nd 1.6 is anaplastic ependymoma (supratentorial)	STR (n=1) 2nd = Total Resection	Pre-radiation chemother apy (n=1) 2nd pt also had CT.	No tumour progression/ relapse 2nd pt did relapse & received further surgery and RT post relapse.	Present in 100% of pts (n=1 or 2)	60 cobalt grey equivalent by 3 dimen-sional conformal proton therapy 2nd pt received 54.8 Gy, photon beam.	Not stated	• Munster Heidelberg Abilities Scale (Fertigkeienskale Munster-Heidelberg [FMH]] scale) • Youth Self report • Childhood behaviour checklist • School Performance	1st Pt in 25-50 percentile for FMH 2nd in 10-25 percentile IQ impairments not stated	• School Performance-Not clear • PedsQL-69 6 • FMH-25-50 percentile. • 3 3 year follow up. • No tumour progression/relapse	3b

Table 2 Continued

Refs.	No of Pts with EPD	Age at Irradiation	Grade & Site	Non radiological treatments		Residual Disease	Hydro-cephalus	Interven-tion (radiation dose)	Survival rate	Psychometric Tests	Impairment	Core Outcomes	Level of Evi-dence
				Surgery	Chemo-therapy								
										PedsQL (parent-rated)			
Von Hoff, *et al.* (2008) [26]	3 All 23 pts had ependymoma - 3 of these were irradiated under 36months A further 1 was irradiated at 3yrs	< 36 months (exact ages not stated) 10 diagnosed under 5yrs - 3 of these irradiated before age 3, 8 irradiated under 5	Infratentorial (n=3)	GTR (n=3)	A no of pts underwent pre-radiation chemo-therapy (exact no unknown) Chemo-therapy according to BBSFOP protocol (Carboplatin / Procarbazin; Etoposide/ Cisplatin; Vincristine/ Cyclophos-phamide)	Not mentioned Normal neurology (n=1) Cerebellar signs: Grade 2 (n=1) Grade 3 (n=1)	Present in 100% of pts (n=3) Or 16/ all 23 pts	50-62 Gy, adminis-tered in 5 weekly sessions of 1.8 Gy per day.	Not stated	• IQ- WPPSI-R. (though 1 pt was too young so received Kaufman-Assessment Battery for Children) 2 groups: <5 yrs; >5 yrs (WISC-III and WAIS-R used for older Pts)	• Below are Pts listed as been more than 2 SD below the mean on the following domains: - • FSIQ 2/23 Pts • 0/23 for verbal IQ • 6/23 for performance IQ Several subtest and other scores listed in relation to deviation from mean. Of the verbal subtests of WISC-III 2/23 more than 2 SDs below mean 1/23 for vocabulary and 4/22 for memory 2	•Tests performed longitudinally. • Not specific about how frequently, but last test recorded were 1.9, 15.3 & 15.6 years after RT, and IQs at last test were 85, 75 & 70, respectively. •There was no sig age dependent decrease in intellectual functions. However there was a trend for worse outcome in younger children. •Suggest that local posterior fossa RT is unlikely to be only factor causing worse neuropsychological outcome in young children. Due to small no of pts, unable to draw any definitive conclusion about role of very young age.	2c
Merchant, *et al.* (2005) [27]	48 All 88 pts in study had ependymoma, 48 were irradiated <36months	<36 months (exact ages not stated)	Infratentorial (n=42) Supratentorial (n=6) Anaplastic (n=22) Differentiated (n=26)	GTR (n= 40) NTR (n= 4) STR (n= 4)	Pre-radiation chemother apy (n=11)	Not mentioned	Present in 83% of pts (n=40)	54Gy n= 12 59.4 Gy n= 36	Not stated	IQ- WPPSI before CRT and at 6, 12, 24, 36, 48 & 60 months after treatment	NA	• Developed a model for estimating IQ- found age at CRT to be a good predictor. (But doesn't explicitly describe differences between <3yrs and >3yrs). • Found that radiation dosimetry remains the most clinically significant determinant of IQ outcomes, and that further reduction in the brain volume that receives the highest doses is warranted.	2c
Merchant, *et al.* (2004) [8]	48	<36 months (exact ages not stated)	Infratentorial (n=42) Supratentorial (n=6) Anaplastic	GTR (n= 40) NTR (n= 4) STR (n	Pre-radiation chemother apy (n= 11)	13 pts < 3 yrs experienced disease progression There were no	Present in 83% of pts (n=40)	54.0-59.4 Gy (1.8 Gy per day)	3yr Progress ion Free Survival estimate 74·7%	•Bayley Scale of Infant Development-II • WPPSI-R. •WISC III	Mean scores on all neurocogni-tive outcomes were within normal limits	• Pts <3 yrs at CRT had sig lower mean IQ at start of CRT than pts >3 yrs, but the IQ of pts <3 yrs improved over time.	2c

Table 2 Continued

Refs.	No of Pts with EPD	Age at Irradiation	Grade & Site	Non radiological treatments		Residual Disease	Hydro-cephalus	Interven-tion (radiation dose)	Survival rate	Psychometric Tests	Impairment	Core Outcomes	Level of Evi-dence
				Surgery	Chemo-therapy								
			(n=22) Differentiated (n=26)	=4)		differences in PFS estimates between pts >3yrs & pts <3yrs at time of RT (or between infratentorial and supratentorial tumours)			+/- 5·7% (Ependy moma only paper)	•WAIS III •California Verbal Learning Test: Child version •Wechsler Individual Achievement Test •Vineland Adaptive Behaviour Scale Survey •Visual-Auditory Learning Test Testing performed before CRT and at 6, 12, 24, 36, 48 & 60 months after treatment.	(i.e. no more than +10 points from normative mean for age group'.	• No sig differences in IQ scores for pts with infratentorial or supratentorial tumours. At 60 months post treatment, mean scores on all neurocognitive outcomes were within normal limits	
Suc, *et al.* (1990) [28]	5	8, 17, 18, 24 & 27 months at diagnosis	Infratentorial (n=5)	GTR (n=4) STR (n=1)	No chemother apy.	Not mentioned	Increased intracranial pressure or hydro-cephalus present in 100% of pts (n=5)	Infraten-torial 45 Gy in 2 pts Infraten-torial 40 Gy in 1 pt Entire neuroaxis (30 + 20) Gy in 1 pt Entire neuroaxis (30 + 22) Gy in 1 pt	5yr survival rate of all (98) infants was 20% - paper is only about the 20 survivors though	• Academic performance • Retrospective study into long-term survivors.	Academic performance for the 5 ependymoma Pts: 2 'retardation' 2 'special education classroom' 1 'normal' No exact scores listed * Also regarding classifications written in 1990*	• Academic performances: - Normal n=1 - 'Special education classes' n=2 - 'Retardation' n=2 • "High rate of mental sequelae is consistent with the concept that XRT is very hazardous before the age of 3".	2c

General: EPD, Ependymoma; GTR, Gross-total resection; NA, Not Applicable; NTR, Near-total resection; Pts; participants; STR, Sub-total resection.

Tests: BSID: Bayley Scales of Infant Development II; BOT-II, Bruininks-Oseretsky Test of Motor Proficiency; California Verbal Learning Test, CVLT; CBCL, Childhood Behaviour Checklist; FMH, 'Fertigkeienskale Munster-Heidelberg' (FMH): Munster Heidelberg Abilities Scale; KABC-II Kaufman Assessment Batter for Children, 2nd Edition; PedsQL, Paediatric Quality of Life Inventory; TEA-Ch, Test of Everyday Attention for Children; VABS, Vineland Adaptive Behaviour Scale Survey; VALT, Visual-Auditory Learning Test; WAIS III, Wechsler Adult Intelligence Scale; WAIS-R, Wechsler Adult Intelligence Scale Revised; WIAT/WIAT II, Wechsler Individual Achievement Test; WISC III/IV: Wechsler Intelligence Scale for Children; WISC-R, Wechsler Intelligence Scale for Children- Revised; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence- Revised; YSR, Youth Self Report.

Table 3: Retrieved Studies of Children <60 Months Diagnosed with Ependymoma Receiving Radiotherapy

Refs.	No of Pts with EPD	Age at irradiation	Grade & Site	Non radiological treatments		Residual Disease	Hydro-cephalus	Interven-tion (radiation dose)	Survival rate	Psychometric Tests	Impair-ment	Core Outcomes	Level of Evi-dence
				Surgery	Chemotherapy								
Di Pinto, *et al.* (2010) [31]	All 71 pts	Mean = 5.59 (SD 3.82) Range = 1.06 - 15.37 37 were under 5 at CRT.	Infratentorial (n=52) Supratentorial (n=19) Tumour laterality: Midline (n=49) Left (n=9) Right (n=13)	All 71 pts GTR or NTE (n=65) STR (n=6)	15/71 pts (Pre RCT chemotherapy)	Pts who experienced treatment failure were not included	Present in 48/71 pts (68%)	54 - 59·4 Gy Pts <18 mths dose = 54·0 Gy (1·8 Gy/day)	Not stated	• Neurocognitive testing: - verbal learning (California Verbal Learning Test-Children's Version) - visual learning (Visual-Auditory Learning Test) • Intellectual function estimates: - mental index of the Bayley scales or 3 subtest administration of age-appropriate Wechsler scale. • Testing performed before CRT, 6 months after CRT and yearly after CRT for 5 years.	Not stated - individual pt results not included in paper	• Younger age tended to predict lower scores at baseline as well as smaller rates of increase in learning scores over time. • Increased vulnerability for younger children at both the start of treatment and after treatment as evidenced by a diminished rate of learning following CRT. • Visual auditory learning more susceptible to disruption in children with localised ependymoma after CRT.	2c
Conklin, *et al.* (2008) [32]	All 87 Pts had EPD,	<5 yrs at irradiation Mean age of all 87 pts at CRT = 5.99 yrs (range 1.06-18.87 years; SD 4.46) 44/87 pts were irradiated under 5 (51%)	Infratentorial (n=65) Supratentorial (n=22)	GTR (n=71) NTR (n=9) STR (n= 7)	Chemotherapy (n=18) Most CT regimens were multi-agent chemotherapy including Cyclophosphamide & Cisplatin or Carboplatin, Etoposide & Vincristine.	Not mentioned	Present in 63% of pts (n=55)	59·4 Gy 54 Gy in pts <18 months. (1·8 Gy/day)	Not stated	• Academic testing not possible in pts <5, though WIAT reading scores were taken • IQ - WPPSI-R. • Testing performed at start of CRT, 6 months after then annually. Median length of follow up was 59.6 months.	Not stated	• Younger age at CRT was predictive of a significant decline in reading over time. • Younger age at CRT was predictive of a significant decline in reading over time. • Math and spelling performance remained stable over time. Reading more vulnerable.	2c
Merchant, *et al.* (2004) [29]	59 pts of all ages had ependymoma	Median age of 4.1 years (range 1.06- 22.92 years) at irradiation All received RT - unclear how many were under 5	Infratentorial (n=59) Anaplastic (n=14) Differentiated (n=45)	GTR (n= 45) NTR (n=5) STR (n=9)	Pre-CRT chemotherapy (n=13)	In no patient was there residual tumour volume greater than 1.2 cm3 at the time of RT	Present in 85% (n=50)	54-59·4 Gy Pts <18 mths dose = 54·0 Gy (1·8 Gy/day)	Not stated	• IQ- Bayley Scale of Infant Development • WPPSI-R. • Testing performed before and 6, 12, 24, 36 and 48 mths after RT.	Not stated	• No significant cognitive decline even among pts <3 yrs were found during a median follow-up period of more than 3 yrs. • (did find that management of hydrocephalus influenced outcome)	2c

Table 3 Continued

Refs.	No of Pts with EPD	Age at irradiation	Grade & Site	Non radiological treatments		Residual Disease	Hydro-cephalus	Interven-tion (radiation dose)	Survival rate	Psychometric Tests	Impair-ment	Core Outcomes	Level of Evi-dence
				Surgery	Chemotherapy								
Van Veelen-Vincent, *et al.* (2002) [30]	All 83 pts had ependym-oma 39/83 pts (47%) were ≤3yrs.	<3 years (though at what point e.g. diagnosis/irradiation not stated) Mean age at diagnosis 36 months (44/83 pts (53%) underwent radiotherapy)	Of all 83 pts: 65 infratentorial 18 supratentorial	Of all 83 pts: GTR (n=60) STR (n=21) Biopsy (n=2)	Of 44pts who underwent RT: 8 received additional chemotherapy. 36/total 83 had chemotherapy	Not mentioned	Present in 67% of all 83 pts (n=56)	50-55 Gy	Overall survival (intra-operative deaths excluded) 5yrs - 73 +/- 11%, 10yrs +/- 14% Event free survival 5yrs - 48 +/-12%, 10yrs 46 +/- 12%	• Academic performance and IQ tests. • Mean follow-up period was 70 months, ranging from 4-217 months.	Mean IQ for all pts was 89±20 (Range 48-131). No individual scores reported	• There was no relationship between IQ and the patient's age at presentation or any type of adjuvant therapy. (Though info about school performance only available in 46 pts, and in 27 of them an IQ was known).	2c
Kieffer-Renaux, *et al.* (2001) [33]	1pt	39 months at irradiation.	Fourth ventricle. Lower pole of tumour extended down to C2. Tumour adherent to lateral part of inferior and medial left cerebellar peduncles. Cisterna magna partly filled by tumour that displaced the vermis upward and amygdala laterally.	Macroscopically complete surgical excision performed. Second partial surgery following non-response to chemo-therapy.	Chemotherapy-baby chemotherapy protocol of the French Society of Pediatric Oncology for 1 ½ years (This comprises 7 cycles of 3 courses administered in an out-patient setting every 3 weeks. Course A is Carboplatin on day 1 and Procarbazine on days 1 to 7. Course B is Etoposide & Cisplatin on days 1 & 2. Course C is Vincristine & Cyclophosphamide on day 1).	6 months after the end of RT, she was admitted for a suspicion of relapse. CT scan showed bilateral calcifications in the cerebellum, temporal & occipital lobes, but no relapse.	Present in 100% of pts (n=1).	55Gy to whole posterior fossa (1·8 Gy/day, 5 days per week, for 5 weeks).	100% (1 pt)	• IQ- WPPSI-R • Memory Efficiency Battery • Language & visuo-spatial skills- Kaufman Assessment Battery for Children	'Marked intellectual impairment' at two testing points FSIQ - 51 then 47 Verbal IQ - 62 then 62 Perform-ance IQ - 48 then 41	• 2 years after RT- major deficit of visual attention, speech was dysarthric, showed marked slowness for adapted behaviour, comprehension and gestural skills. • IQ- WPPSI-R - 51 • 4 years after RT- WPPSI-R stable. Distractibility decreased and lang. ability improved. • Overall- signs of visual agnosia and marked intellectual impairment	3b

General: CSI-Craniospinal irradiation; EPD, Ependymoma; GTR, Gross-total resection; NA, Not Applicable; NTR, Near-total resection; Pts, participants; STR, Sub-total resection

Tests: BSID: Bayley Scales of Infant Development II; California Verbal Learning Test, CVLT; KABC-II Kaufman Assessment Batter for Children VALT, Visual-Auditory Learning Test; WAIS III, Wechsler Adult Intelligence Scale; WAIS-R, Wechsler Adult Intelligence Scale Revised; WIAT/WIAT II, Wechsler Individual Achievement Test; WISC III/IV: Wechsler Intelligence Scale for Children; WISC-R, Wechsler Intelligence Scale for Children- Revised; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence- Revised

and cyclophosphamide (VEC) +/- second look surgery followed by the described radiotherapy (RT) protocol were given. After 2001, patients with complete resection and Grade II revised histology had CRT with conventional fractionation of 1.8 Gy/d. Patients with complete excision and Grade III revised histology received four VEC courses after RT. With residual tumour of any grade VEC was given before RT to facilitate second look surgery. In [22, 24] no detailed RT protocol is described but presence and complexity of hydrocephalus with required treatment is given [22]. For [23] adjuvant treatment was planned to start within four weeks of surgery and followed two different treatment protocols. In regimen I (1994-2003) four blocks of vincristine (1.5 mg/m^2) plus high-dose methotrexate 5g/m^2 with cyclophosphamide 1.5 g/m^2 alternating with cisplatin 90 mg/m^2 plus VP16 450 mg/m^2 for year one. Regimen II included VEC: VCR 1.5mg/m^2 plus VP16 300mg/m^2 and CTX 3g/m^2 for six months. CT was discontinued following disease progression. RT was planned only for patients with residual tumour after CT or progression of tumour while receiving CT. RT doses and schedules varied according to the used protocol: hyperfractionated RT (1.1 Gy twice a day) administered to the tumour bed with a 1-2 cm margin (margin reduction was adopted during that time according to physicians' experience and literature), up to 70.4 Gy for children treated before 2001, or conformal RT using conventional fractionation of 1.8 Gy a day up to a total of 54-59 Gy after 2001. Post operative and pre-irradiation MRI defined the residual disease and possibly collapsed post-surgical tumour bed. The planning target volume was 0.5 cm larger than the clinical target volume in all directions. No reduction of fields or radiation boost was planned in case of residual tumour. No detailed information regarding RT is provided in [25]. For [26] total dose ranged from 50-62 Gy, administered in five weekly sessions of 1.8 Gy per day. For patients early in the series, radiographic simulation images with hand-drawn tailored shielding based upon physician knowledge of anatomical structures and tumour characteristics were used. For those treated later, 3D high definition CT-based representation of dose-distribution superimposed with posterior fossa structures and tumour contour were available. The GTV for the primary site boost included the post-operative tumour bed. The CTV included in the GTV with an anatomically confined margin of 2 cms in the adjacent brain whereas the PTV expanded the CTV with a geometric margin of 1 cm. Multiple beam arrangements were used. Their initial approach induced full dose to the entire posterior fossa including occipital and posterior temporal areas. Only the pituitary area located at the anterior margin was kept to an 'acceptable' level. The later approach permitted reduced maximal dose to most structures outside the posterior fossa. Papers [8, 27] present the same patients. The GTV contained the tumor bed, residual tumor, or both. The CTV contained the GTV with an added margin of 1 cm, which was included so that subclinical microscopic disease beyond the GTV could be treated. The CTV was anatomically confined; that is, it was limited by normal tissue structures through which tumor extension was unlikely. The planning target volume included the CTV surrounded by an additional margin of 3 to 5mm, expanded in three dimensions to account for uncertainty in patient positioning and image registration. Conventional fractionation (1.8 Gy per day) was used to treat all patients, and the prescribed dose was 59.4 Gy. Exceptions included children younger than 18 months and three children older than 18 months who received 54.0 Gy after gross-total resection. For [28] minimal data regarding RT is provided.

Mortality and Neurocognitive Morbidity

Typically, survival rates were not stated. When they were included (33.3%; 3/9) the calculation had been completed for all patients (of any age at irradiation or any tumour type in mixed studies) and ranged from 20% at five years [28] and 74.7% at three years [8]. A total of 13 different psychometric tests were used (excluding editions of the same test e.g. WISC III and WISC IV were classed as one test, three of which were proxy measures - CBCL, PedsQL and VABS). Five studies used Wechsler ability measures (WPPSI, WPPSI-R, WISC-III, WISC-IV, WAIS-R and WAIS-III to obtain IQ [7,8,22,26,27]. Three studies [23,25,28] reported IQ scores and/or scholastic performance with no indication as to how this was obtained. One study stated that patients who were not irradiated did not demonstrate better outcomes than those who were [23]. Another indicated that radiation dosimetry was the most clinically significant determinant of IQ outcome [27] with a further [28] agreeing that radiation before 36 months was 'very hazardous' for mental sequelae. One study suggested that radiotherapy was unlikely to be the only factor contributing to poor neurocognitive outcome in young children [26]. A further paper [7] suggested that tumour location and pre-/perioperative damage seemed to affect cognitive outcome more than age at RT.

DISCUSSION

This systematic literature review has identified only limited data from published studies regarding morbidity and mortality of post surgical irradiation. There is significant scope to develop a better evidence base and improve neurocognitive assay.

Sixty-six children under 36 months received radiotherapy with 80% (53/66) of these children receiving infratentorial radiotherapy and 14% (9/66) supratentorial radiotherapy. For the remaining children, anatomical site was not specified. One child was irradiated (infratentorial) at <12 months. Of 14 papers reaching minimum quality standards, nine papers indicated radiotherapy for childhood ependymoma leads to lower IQ scores or poorer overall cognitive outcome [22, 27, 28, 31, 33, 35, 37, 42, 44] compared to norms. One of these studies [28] suggested that young age at CRT is a further risk factor with Di Pinto *et al.* [31] stating that young age at irradiation leads to smaller rates of increase in learning over time and Kieffer-Renaux *et al.* [37] noting that IQ continues to decline more than four years post diagnosis. Conklin *et al.* [32] identify that young age at CRT affects reading ability with Pulsifer *et al.* [44] finding significant decline in processing speed and visual-spatial organisation in childhood ependymoma survivors. In contrast, six of the retrieved papers stated CRT does not predict poorer cognitive outcomes [7,23,29,30,36,41]. Further to this, Merchant and colleagues [8] state that being less than 36 months old at time of radiotherapy may lead to lower IQ but that this is a product of the tumour itself and following CRT, cognition may improve over time. It is important to note that improvements may well occur but as a consequence of the normal neurodevelopmental process. What remains unclear is whether the rate of new learning and skill acquisition post CRT is commensurate with typical cognitive trajectories. Poggi *et al.* [39] found that young age (0-6yrs) at radiotherapy leads to lower cognitive impairment. Young age and CRT may not be the only factors leading to a reported decline in cognitive function. For example, cognitive deficits or low IQ may be predicted by radiation dosimetry [27], tumour location [7,42]; pre- or perioperative brain damage [7] or presence of lacunae [38]. The presence and management of hydrocephalus are also implicated as factors effecting cognitive outcome [29]; however, Davis *et al.* [22] did not replicate this finding with no consistent effect of hydrocephalus on outcome demonstrated. Where IQs are reported, large inter-individual differences [22] were present with no definitive explanation provided accounting for this variability.

Twenty-five papers were found to include childhood ependymoma patients who had received radiotherapy as treatment. In comparison to the wealth of studies available for mortality rates, there is a paucity of work describing cognitive morbidity for irradiated survivors of childhood ependymoma. Of the few studies that investigated this and are consequently included in this review, a majority were rated at 2b for quality of evidence [20]. In all but one of the twenty-five studies reviewed, the number of ependymoma patients could be identified clearly. However, determining patient age at diagnosis, treatment or follow-up was not straightforward. Scrutiny of retrieved papers led to three categories of data emerging. Nine papers (Table **2**) stated explicitly that patients were irradiated for ependymoma at <36 months. Five references (Table **3**) included patients who received radiotherapy for an ependymoma at <60 months. Therefore, some of these patients may have been <36 months but this information could not be ascertained. Finally, eleven papers (Supplementary Table) presented children who were treated with radiotherapy for ependymoma but age was not specified. Data were of variable quality. Where ependymoma patients were clearly identifiable their numbers ranged from 1-88. Those that included ependymoma patients only led to more accessible data. In papers where more than one brain tumour type was discussed, data regarding irradiation outcomes for ependymoma were more difficult to access.

Methodological limitations are present in the retrieved papers. There is inconsistency for data reporting ensuring comparisons and more standard forms of statistical scrutiny cannot presently be performed. The use of psychometry was an inclusion criterion for papers in this review and, therefore, all papers discussed make reference to some form of neurocognitive assessment and outcome. However, there are inconsistencies across the retrieved papers for the measures used and the way in which obtained results were reported. Across all studies, 16 different measures were used to explore neurocognitive functioning in differing combinations. Some commonality occurs with 69·6% (18/25) of papers using a Wechsler test to establish IQ. In three studies IQ is stated but no information is given regarding how this was obtained. Four papers discuss vague descriptions of scholastic outcomes.

Comparisons cannot be made across all papers, as there is a lack of sufficient data delineation and stratification. Some papers (e.g. [22]) compare the outcomes of irradiated ependymoma survivors according to neurological results such as 'presence/absence' of hydrocephalus. They also include the numbers of patients who received radiotherapy but do not compare results according to treatment received, possibly due to small sample size. Hydrocephalus has been identified as a potential risk factor for cognitive decline following a brain tumour such as ependymoma [29] but its presence or absence was only reported in 68% (17/25) of the studies. Other reasons for poor outcomes are included within studies variably. For example, radiation dosimetry is well reported (22/25 studies) as is tumour location in 19/25. The main issue with this information is that it cannot be specifically identified for ependymoma patients and, therefore, conclusions cannot be drawn. Publishing of individual data via supplementary tables may help to improve analysis to ensure accurate neurocognitive prognosis for this group. The benefits of this approach have been demonstrated with other neurocognitively impaired paediatric groups e.g. [45,46].

Given the likely role of the cerebellum in cognitive development and the demonstrated variability in the neurocognitive outcomes for this group, it is not presently possible to be confident that these children will be unaffected in the long term. Current evidence indicates the cerebellum is involved in the construction and organisation of higher cognitive functions and social behaviours [47] typically associated with the prefrontal cortex. This reflects the integrated network of neural inputs into the cerebellum from all levels of the CNS, including spinal, vestibular and cerebral pathways. Damage to the cerebellar hemispheres has been shown to be associated with intellectual changes, with damage to the vermis associated with behavioural changes [13]. Reciprocal projections between the cerebellum and cerebral cortex provide a plausible neuroanatomical basis for a cerebellar role in cognition [47]. While damage to either cerebellar hemisphere produce ipsilateral motor deficits, projections from the cerebellum to the cerebral cortex are contralateral. Consistent with this structural organisation, evidence indicates lateralized cerebellar lesions produce cognitive deficits similar to those observed following lesions of the contralateral cerebral hemisphere [48]. It is hypothesized that this may be caused by disruption of the metabolic activity to cerebello-cortical pathways [49,50]. Therefore, verbal functions and/or literacy deficits, in right-handed individuals, have been associated with right cerebellar damage and visuospatial deficits with left cerebellar damage [13]. Because of the increasing role attributed to the cerebellum in higher cognitive functions [15] and acquisition of literacy [12,14], cerebellar dysfunction secondary to the tumour and its treatment(s) is implicated as having a major detrimental effect on intellectual, cognitive, learning and functional outcomes [51].

Although the retrieved papers testify to the importance of assessing neurocognitive outcomes, it is critical to note that no clear neurodevelopmental model is ever presented to account for the findings. This is concerning as its omission limits a complete and long-term understanding of cognitive development and its impairment or indeed resilience for this group of children. The timing of acquired damage, the period of cognitive development and brain maturation all provide the potential for demonstrated adverse 'downstream effects' on yet to be acquired skills, such as literacy and later cognition [52]. The recognition of a primary damage leading to later manifesting secondary impairments ensures the need for long-term prospective surveillance of neurocognitive outcomes. For example, as modest associations exist between developmental tests and later IQ [53], it is inappropriate to draw definitive conclusions regarding patients' likely cognitive abilities and learning outcomes in later life from measures used in early childhood. In addition, the maximum length of follow-up for ependymoma patients was 60 months post treatment [8]. Thus, if the patient was 36 months when receiving radiotherapy their maximum age at follow-up would be eight years. This period of follow up has created the claim [3] that learning in these children remain unaffected. 'Mechanical' literacy skills i.e. reading accuracy and spelling, continue to develop beyond eight years of age [54] with the comprehension of read materials becoming increasingly important. Some papers (e.g. [8]) provide the mean scores for the reading accuracy and spelling components of literacy. Reading comprehension remains unassessed. A child learns to read, then reads to learn. If acquisition of literacy is impaired then all that flows from this will be affected similarly. Impaired literacy acquisition across childhood can adversely affect IQ in the long-term [55]. From Table **2**, only 4/9 studies examine literacy in different and incomplete ways. Given the evidence for cerebellar involvement in the acquisition of literacy, more detailed prospective assay of reading is now required. Cognition and learning continue to unfold beyond eight years of

age and outcomes beyond this remain unknown. In addition, there is evidence that children who are initially assessed as without difficulties may develop significant later, more global, impairments to cognitive functioning due to the phenomenon of 'growing into deficit' [56]. With improved follow-up and consistent neurocognitive assay, treating and research communities may be better able to substantiate the claim for an absence of adverse neurocognitive sequelae for irradiation at <36 months. While a complete absence of late neurocognitive effects may not be a realistic aim, the aim to address methodological variation and inconsistent capture of neurocognitive outcome is.

Sample size varies and data collection is retrospective or prospective. The technique of RT used; timing of RT; role of multiple surgery and presence of cerebellar mutism are described variably. In [8] patients were treated with post-surgical RT for initial management. For [23] most received RT as part of a salvage strategy including repeat surgery. Multiple resection and anticipated and non-anticipated post-neurosurgical complications may restrict clarity of conclusion further. Given the variability of data presentation and differing opinions regarding the role of RT in neurocognitive sequelae it is recommended that data capture should be standardised. To better establish the longer-term risk for this group, data collection for the following are suggested: presence of cerebellar mutism, tracheostomy rates; vascular events; number of days in PICU; number of surgeries performed; presence of residual disease; premorbid difficulties; ability and literacy outcomes, using Wechsler tests.

Claims [8,19] for the absence of long-term neurocognitive impairment in childhood ependymoma (3 years of age) require further evaluation as retrieved evidence questions this view. From retrieved evidence, considerable variability in neurocognitive outcome is demonstrated for children who received radiotherapy for ependymoma at this age. The retrieved papers raise the question of the type of data needed by the treating and research community to fully understand the long-term neurocognitive consequences of ependymoma and their treatments. Without this, the actual morbidity and the full costs of long term neurodisability, unemployment and underemployment will never be known. This paper only reviews the reported neurocognitive sequelae of photon radiotherapy for young ependymoma patients. As proton radiotherapy is increasingly being used it is important to address consistency of methodology and data reporting. Although at present it may not be possible to achieve consensus for international clinical practice, it is crucial to establish a common agreement for study design; neurocognitive development, learning and its measurement; consistency and delineation of data capture and reporting, and duration of follow-up, to allow systematic comparisons across studies to be made. The International Society for Paediatric Oncology (SIOP) is currently working towards this.

CONFLICT OF INTEREST

No conflict of interest is declared.

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