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ORIGINAL ARTICLE

Neurocognitive, academic and functional outcomes in survivors of infant ependymoma (UKCCSG CNS 9204)

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Abstract

Purpose This is the first UK multi-centre case-controlled study with follow-up in excess of 10 years to report the neurocognitive, academic and psychological outcomes of individuals diagnosed with a brain tumour in early childhood. Children enrolled into the UKCCSG CNS 9204 trial, diagnosed with intracranial ependymoma when aged ≤ 36 months old, who received a primary chemotherapy strategy to defer or avoid radiotherapy, were recruited.

Methods Outcomes of those who relapsed and subsequently received radiotherapy ($n = 13$) were compared to those enrolled who did not relapse ($n = 16$), age-matched controls—diagnosed with solid non-central nervous system (SN-CNS; $n = 15$) tumours or low-grade posterior fossa pilocytic astrocytoma (PFPA; $n = 15$), and normative data. Analyses compared nine neurocognitive outcomes as primary measures with quality of survival as secondary measures.

Results Relapsed ependymoma participants performed significantly worse than their non-relapsed counterparts on measures of Full Scale IQ, Perceptual Reasoning, Word Reading and Numerical Operations. The relapsed ependymoma group performed significantly worse than SN-CNS controls on all primary measures, whereas non-relapsing participants only differed significantly from SN-CNS controls on measures of Processing Speed and General Memory. Relapsed ependymoma participants fared worse than all groups on measures of quality of survival.

Conclusions The relapsed irradiated ependymoma group demonstrated the most significantly impaired neurocognitive outcomes at long-term follow-up. Non-relapsing participants demonstrated better outcomes than those who relapsed. Results tentatively suggest avoiding radiotherapy helped preserve neurocognitive and learning outcomes of individuals diagnosed with ependymoma when aged ≤ 36 months old. Prospective neurocognitive surveillance is required. Recommendations for clinical and research practice are provided.

Keywords Brain tumour · Ependymoma · Paediatric · Outcome · Neurocognitive · Quality of survival

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Introduction

Ependymoma accounts for 5–10% of all paediatric brain tumours in the UK [1]. It is predominantly an infantile tumour; 50% of cases occur in individuals less than 5 years of age in the UK [1] and around 30% in children < 3 years old in the USA [2]. A five-year survival rate for ependymoma was 71% from 2006 to 2010 in the UK [3]. With increased survival, clinicians have become more aware of the late occurring adverse effects of the tumour and its treatments, particularly neurocognitive impairment [4]. The neurocognitive late effects, defined typically as intellectual and learning impairments, are associated with paediatric brain tumours and are an area of expanding clinical and research interest [5, 6].

Although the principal treatment for ependymoma is neurosurgery, adjuvant therapy is required [7]. Decisions over

optimal adjuvant therapy are contentious due to radiotherapy and chemotherapy having accompanying risks for brain function with this risk heightened when it involves an immature developing brain [1]. Certain studies have demonstrated the negative impact of craniospinal irradiation and chemotherapy on myelination and development of white matter and the significant detrimental impact this has on cognition, especially processing speed, as early as 36 months post diagnosis [4, 8]. The most effective treatment of ependymoma in children < 3 years old remains controversial with differences existing between the approaches used in Europe and North America.

European practice typically followed protocols such as the 'Baby Brain' protocol [9], devised to avoid or defer detrimental and potentially irreversible damage caused by administering radiotherapy at such a sensitive stage of brain development. Neurosurgery and chemotherapy are the initial treatments in these protocols with radiotherapy administered once, only if relapse occurs. Studies demonstrate that chemotherapy strategies are successful and avoiding or deferring radiotherapy is possible in the infantile ependymoma population without compromising survival [10]. Overall published survival rates at 5 years were 37% [11], 52% [12] and 60% [10].

Some USA centres administered radiotherapy to infant brains, following findings such as those by Merchant et al. [13] who found significantly reduced mean IQ of 89.7 ± 2.8 in children irradiated ≤ 3 years old compared to those older than this but reported that aggregate scores improved over time. At latest follow-up, all neurocognitive outcome scores were within 'normal' limits, being no more than 10 points from the normative mean. Progression free survival at a median follow-up length of 38.2 months (range 12.4–75.6 months) was reported as 73% in the study, with 13/48 (27%) patients irradiated under the age of 3 years having disease progression [13]. This was greater than studies deferring radiotherapy in individuals under 3 years, who reported actual 3-year progression free survival of 27% [11] and 43% [10]. As a result of prospective data from the recent ACNS0121 trial, immediate postoperative radiotherapy for children with ependymoma as young as 12 months old has been advocated by the Children's Oncology Group [14].

Conflicting information regarding the impact of radiotherapy produces uncertainty about optimal treatment conferring least mortality. Variability in neurocognitive tests used and time points for follow-up in previous studies means further evidence is needed to support the assertion that neurocognitive detriments are limited when post-surgery radiotherapy for ependymoma is administered ≤ 36 months old [15].

A UK multi-centre study determining the long-term neurocognitive outcomes of a paediatric brain tumour clinical trial has not been reported previously. The present study aimed to follow-up children who were enrolled into the UKCCSG CNS 9204 trial, diagnosed with an intracranial ependymoma and treated with the 'Baby Brain' protocol from 1992 to 2003 when ≤ 36 months old, to determine their neurocognitive, educational, psychosocial and functional/adaptive outcomes. Individuals who relapsed and received radiotherapy were compared to those who did not.

Additional comparisons were made against two control groups diagnosed with paediatric cancerous tumours, matched by age at assessment, gender and age at diagnosis with the ependymoma groups. Control groups consisted of low-grade PFPA treated with neurosurgery only and solid non-central nervous system (SN-CNS) tumours receiving no central nervous system (CNS)–directed treatments. Controls permitted inferences regarding neurocognitive and functional outcomes following diagnosis of a paediatric brain tumour: specifically, whether differences in outcomes were observed between groups treated with different CNS targeted treatments (neurosurgery, chemotherapy and/or radiotherapy) and when compared to outcomes following paediatric non-CNS tumours. Hypotheses were:

- The non-relapsed ependymoma group would have better neurocognitive outcomes than the relapsed group.
- The chemotherapy protocol and resultant delay in receiving radiotherapy would be successful in improving quality of survival.
- Both relapsed and non-relapsed ependymoma groups would demonstrate worse outcomes than the control groups.
- The SN-CNS control group would have better outcomes than the other groups.

Methods

Participants and study design

All 17 UK centres taking part in the CNS 9204 trial were requested to participate. Patients enrolled in the UKCCSG CNS 9204 trial diagnosed with an intracranial ependymoma ≤ 36 months old were invited to participate. There were 51 survivors with 29 recruited. Within recruited participants, n = 13 had relapsed and received radiotherapy and n = 16 had not. Mean age at diagnosis for all individuals diagnosed with ependymoma was 2 years (SD 0.8; range 0.34–3.5 years). In the additional 22 survivors, n = 10 failed to respond to study invitation, n = 7 declined to participate and n = 5 agreed to participate but were lost to follow-up.

Invited controls consisted of individuals with SN-CNS tumours with no CNS-directed treatment and individuals with low-grade PFPA treated with neurosurgery alone. These groups were matched as closely as possible to ependymoma patients for gender, age at testing and age at diagnosis (within 2 years 11 months of both ependymoma groups). When

recruiting controls, presence of a pre- or post-morbid diagnosis which would affect their reliability as a control ensured exclusion. 30 matched controls were recruited; $n = 15$ SN-CNS and $n = 15$ PFPA.

Across the four groups, a total of 59 individuals were assessed. A cross-sectional case-controlled methodology was used. Table 1 provides group descriptive statistics. Total mean follow-up was 11.10 years (SD 5.00; range 2.1–20.46 years). A significant effect of group on mean age at follow-up was observed ($F(3,55) = 3.217$, $p = .030$). Tukey HSD post hoc tests revealed that mean age at follow-up was significantly lower in the PFPA group compared to the ependymoma relapsed group ($p = .021$). No other significant differences in mean age at follow-up were observed between groups.

Procedures

To assess neurocognitive, academic and psychological outcomes, standardised psychometric assessments and self- and parent-rated measures were used. Measures were compliant with European and USA study neurocognitive assessment guidance [16, 17]. Nine primary measures were used: Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed, Full Scale IQ, Word Reading, Spelling, Numerical Operations and General Memory. Secondary neurocognitive and psychological outcomes were also collected (See Online Resource 1 for measures administered and Online Resource 2 for a glossary of measures).

Statistical analyses

Only scores obtained on primary measures and selected secondary measures (Vineland Adaptive Behavior Scales-II; Health Utilities Index (HUI)) were analysed in this study. The Kolmogorov-Smirnov test was applied to determine whether or not data were distributed normally. To determine whether significant differences existed between groups on primary neurocognitive measures, a MANOVA was conducted followed by univariate tests—one-way ANOVAs. Bonferroni correction was applied to correct for multiple tests. Following the identification of significant effects of group on these measures, pairwise post hoc analyses were completed to detect between which groups these differences existed. Post hoc analysis was completed using Tukey's HSD tests. To assess whether each group's scores on the primary measures differed significantly from the normative population, one sampled t tests were employed with Bonferroni correction applied to account for multiple comparisons. Between-group comparisons were made on selected secondary measures using one-way ANOVA with Tukey's HSD post hoc analysis.

Results

Kolmogorov-Smirnov produced no significant differences ($p > 0.05$). Parametric tests were used for subsequent analyses.

Between-group comparisons

Descriptive statistics of primary outcomes are displayed in Table 2. All terms used for primary measures are defined (Online Resource 2).

MANOVA indicated a significant effect of group on the primary outcome measures ($V = .78$, $F(27,135) = 1.742$, $p = .021$) and when followed up using separate univariate tests for each primary outcome measure, significant effects of group were detected for all outcome measures with the exception of Working Memory and Spelling which did not remain statistically significant when Bonferroni correction was applied (alpha value 0.0056 adopted; Table 3). Pairwise post hoc analyses revealed significant differences between groups (Table 4). The ependymoma relapsed group performed significantly worse than all groups on Perceptual Reasoning, Word Reading and Full Scale IQ (ranging from $p < .0001$ to $p = .040$). Compared to controls, the ependymoma relapsed group performed significantly worse than both PFPA and

Table 1 Key descriptive statistics for individual groups; ependymoma, ependymoma relapsed, low-grade posterior fossa pilocytic astrocytoma (PFPA) and solid non-central nervous system tumours (SN-CNS). Note. SD, standard deviation; M, male; F, female

Groups (total $n = 59$)	Gender (M/F)	Mean age at diagnosis (SD)	Range - age of diagnosis	Mean age at relapse (SD)	Range - time of relapse occurrence	Mean age at testing (SD)	Mean length of follow-up (SD)
Ependymoma ($n = 16$)	10 M 6 F	2 years (0.92)	0.34–3.47 years			13.95 years (3.95)	11.95 years (4.27)
Ependymoma relapsed ($n = 13$)	9 M 4 F	2.1 years (0.60)	0.83–2.91 years	4.53 years (2.55)	0.38–10.16 years	15.61 years (3.34)	13.60 years (3.45)
Low-grade posterior fossa pilocytic astrocytoma (PFPA; $n = 15$)	9 M 6 F	4.07 years (2.51)	1.05–11.87 years			12.43 years (3.54)	8.35 years (4.14)
solid non-central nervous system tumours (SN-CNS; $n = 15$)	8 M 7 F	4.01 years (3.81)	1.25–14.36 years			14.76 years (4.61)	10.75 years (6.14)

Table 2 Descriptive statistics for primary outcome measures

Measure	Index	Ependymoma relapsed				Ependymoma				PFPA control				SN-CNS control			
		n	Mean	SD	Clinical interpretation	n	Mean	SD	Clinical interpretation	*n*	Mean	SD	Clinical interpretation	*n*	Mean	SD	Clinical interpretation
WISC-*IV*/*W*AIS-IV	VCI	13	68	16.19	Extremely Low	16	83.63	21.97	Low Average	15	90.53	13.51	Average	15	97.13	11.54	Average
	PRI	13	71.69	18.87	Borderline	16	88.94	20.39	Low Average	15	90.47	15.65	Average	15	99.4	11.13	Average
	WM	13	73.08	13.68	Borderline	16	83.69	19.57	Low Average	15	88.73	16.41	Low Average	15	96	17.88	Average
	PSI	13	65.23	15.63	Extremely Low	16	79.88	17.93	Borderline	15	86.07	11.87	Low Average	15	94.6	15.12	Average
	FSIQ	13	62.62	17.02	Extremely Low	16	80.88	22.01	Low Average	15	86.93	15.18	Low Average	15	96.07	10.55	Average
WIAT-II	Reading	13	63.31	20.88	Extremely Low	16	86.44	22.95	Low Average	15	91.97	21.71	Average	15	100.13	12.46	Average
	Spelling	12	72.08	18.65	Borderline	16	88.5	22.49	Low Average	15	87.13	19.73	Low Average	15	99.87	15.73	Average
	Numerical Operations	12	68.17	22.76	Extremely Low	15	87.73	22.02	Low Average	15	81.47	17.24	Low Average	15	101.4	12.48	Average
CMS-WMS-IV	GMI	11	68.45	14.38	Extremely Low	16	85.6	26.48	Low Average	15	97.07	11.15	Average	15	109.07	15.06	Average

PFPA posterior fossa pilocytic astrocytoma, *SN-CNS* solid non-central nervous system tumour, *WISC-IV/WAIS-IV* Wechsler Intelligence Scale for Children-Fourth Edition/Wechsler Adult Intelligence Scale-Fourth Edition, *WIAT-II* Wechsler Individual Achievement Test-Second Edition, *CMS/WMS-IV* Children's Memory Scale/Wechsler Memory Scale-Fourth Edition, *VCI* Verbal Comprehension, *PRI* Perceptual Reasoning, *WM* Working Memory, *PSI* Processing Speed, *FSIQ* Full Scale IQ, *GMI* General Memory

Table 3 One-way analysis of variance (ANOVA) of primary outcomes for all groups

Measure	Index	Univariate test statistic
WISC-IV/WAIS-IV	VCI	$F(3,55) = 7.982$, $p = .000$*, $r = .55$
	PRI	$F(3,55) = 6.45$, $p = .001$*, $r = .51$
	WM	$F(3,55) = 4.36$, $p = .008$, $r = .44$
	PSI	$F(3,55) = 9.02$, $p = .000$*, $r = .57$
	FSIQ	$F(3,55) = 9.73$, $p = .000$*, $r = .59$
WIAT-II	Word reading	$F(3,55) = 8.54$, $p = .000$*, $r = .32$
	Spelling	$F(3,55) = 4.57$, $p = .006$, $r = .45$
	Numerical Operations	$F(3,55) = 7.24$, $p = .000$*, $r = .54$
CMS/WMS	General Memory	$F(3,55) = 11.44$, $p = .000$*, $r = .63$

F F value, *r* effect size, *WISC-IV/WAIS-IV* Wechsler Intelligence Scale for Children-Fourth Edition/Wechsler Adult Intelligence Scale-Fourth Edition, *WIAT-II* Wechsler Individual Achievement Test-Second Edition, *CMS/WMS* Children's Memory Scale/Wechsler Memory Scale, *VCI* Verbal Comprehension, *PRI* Perceptual Reasoning, *WM* Working Memory, *PSI* Processing Speed, *FSIQ* Full Scale IQ. Asterisks indicate statistically significant effects when Bonferroni correction is applied

SN-CNS groups on measures of Verbal Comprehension, Processing Speed and General Memory (ranging from $p < .0001$ to $p = .004$). The ependymoma relapsed group performed significantly worse than both the ependymoma ($p = .047$) and SN-CNS groups ($p < .0001$) on Numerical Operations and significantly worse than SN-CNS controls on Working Memory ($p = .005$) and Spelling ($p = .003$).

Comparing performance on primary measures between the ependymoma non-relapsed group and control groups, scores for Processing Speed ($p = .047$) and General Memory ($p = .006$) were significantly worse in the ependymoma group compared to SN-CNS controls. The ependymoma non-relapsed and PFPA groups did not differ significantly on any primary neurocognitive measures. The only significant difference in performance observed between control groups on any primary measure was that the PFPA group performed significantly worse on Numerical Operations than the SN-CNS group ($p = .027$).

Examining performance on secondary measures, means from the HUI Participant reported, HUI- Parent/Guardian reported and Vineland II- Adaptive Behavior Composite (and corresponding mean plots; Fig. 1) visually demonstrate increasing quality of survival and independence, respectively, from ependymoma relapsed-ependymoma-PFPA-SN-CNS. A significant effect of group was observed for both HUI Participant reported ($F(3,55) = 5.073$, $p = .004$, $r = .48$) and HUI Parent/Guardian scores ($F(3,49) = 5.585$, $p = .002$, $r = .51$). No significant differences were observed between the ependymoma relapsed and non-relapsed groups on both Participant reported ($p = .319$) and Parent/Guardian HUI scores ($p = .839$). The Ependymoma Relapsed group demonstrated significantly poorer outcomes than PFPA controls on Participant reported HUI ($p = .029$) and a trend for lower scores on the Parent/Guardian reported HUI ($p = .056$). The ependymoma relapsed group demonstrated significantly poorer outcomes than SN-CNS controls on both Participant reported ($p = .003$) and Parent/Guardian reported HUI ($p = .005$). The ependymoma non-relapsed group only obtained significantly poorer outcomes than SN-CNS controls on Parent/Guardian reported HUI ($p = .019$). No significant differences were observed between control groups on either measure.

A significant effect of group was observed for Vineland II-Adaptive Behavior Composite scores ($F(3,55) = 5.315$, $p = .003$, $r = .47$). The ependymoma relapsed group demonstrated significantly poorer scores than both PFPA ($p = .033$) and SN-CNS controls ($p = .003$). No other significant differences were observed between groups.

Comparisons with normative data

Results where groups' performance differed significantly from population norms are shown in Table 5 with asterisks denoting significant differences which withstand Bonferroni correction (alpha level 0.0014 adopted). Scores from the ependymoma relapsed group differed significantly on all measures whilst scores from the ependymoma non-relapsed group only deviated significantly from population norms for Processing Speed. When examining performance of control groups, scores from PFPA controls differed significantly for Processing Speed and Numerical Operations while scores from SN-CNS controls did not differ significantly from population norms.

Discussion

The relapsed ependymoma group had consistently poorer neurocognitive outcomes than all other groups. Mean Full Scale IQ for the relapsed ependymoma group fell emphatically within the impaired range, compared to other groups, whose scores fell within 'low average' to 'average' ranges.

Table 4 Post hoc analyses using Tukey's HSD for group comparisons on all primary neurocognitive measures

Measure		EpR vs. Ep		EpR vs. PFPA		EpR vs. SN-CNS		Ep vs. PFPA		Ep vs. SN-CNS		PFPA vs. SN-CNS	
		Mean difference (95% CI)	*p*	Mean difference (95% CI)	*p*	Mean difference (95% CI)	*p*	Mean difference (95% CI)	*p*	Mean difference (95% CI)	*p*	Mean difference (95% CI)	*p*
	Index												
WISC-IV/WAIS-IV	VCI	− 16 (− 32, 1)	.063	− 23 (− 39, − 6)	.003**	− 29 (− 46, − 13)	.000**	− 7 (− 23, 9)	.647	− 14 (− 29, 2)	.113	− 7 (− 22, 9)	.690
	PRI	− 17 (− 34, − 1)	.040*	− 19 (− 36, − 2)	.024*	− 28 (− 45, − 11)	.000**	− 2 (− 18, 15)	.994	− 11 (− 27, 6)	.321	− 9 (− 25, 7)	.475
	WM	− 11 (− 28, 6)	.358	− 16 (− 33, 2)	.088	− 23 (− 40, − 6)	.005**	− 5 (− 21, 11)	.846	− 12 (− 29, 4)	.203	− 7 (− 24, 9)	.655
	PSI	− 15 (− 30, 1)	.062	− 21 (− 36, − 5)	.004**	− 29 (− 45, − 14)	.000**	− 6 (− 21, 8)	.677	− 15 (− 29, − 0.1)	.047*	− 9 (− 23, 6)	.430
	FSIQ	− 18 (− 35, − 2)	.026*	− 24 (− 41, − 7)	.002**	− 33 (− 50, − 17)	.000**	− 6 (− 22, 10)	.748	− 15 (− 31, 1)	.068	− 9 (− 25, 7)	.451
WIAT-II	Reading	− 23 (− 43, − 3)	.015*	− 29 (− 49, − 9)	.002**	− 37 (− 57, − 17)	.000**	− 5 (− 24, 14)	.873	− 14 (− 33, 5)	.236	− 8 (− 28, 11)	.670
	Spelling	− 15 (− 36, 3)	.132	− 15 (− 35, 5)	.200	− 28 (− 48, − 8)	.003**	1 (− 17, 20)	.997	− 11 (− 30, 7)	.371	− 13 (− 32, 6)	.286
	NO	− 20 (− 39, − 0.2)	.047*	− 13 (− 33, 6)	.275	− 33 (− 53, − 14)	.000**	6 (− 12, 25)	.799	− 14 (− 32, 5)	.206	− 20 (− 38, − 2)	.027*
CMS/WMS-IV	GMI	− 18 (− 37, 1)	.066	− 29 (− 48, − 9)	.001**	− 41 (− 60, − 28)	000**	− 11 (− 28, 7)	.377	− 23 (− 40, − 5)	.006*	− 12 (− 30, 6)	.281

EpR ependymoma relapsed, *Ep* ependymoma, *PFPA* posterior fossa pilocytic astrocytoma, *SN-CNS* solid non-CNS, *WISC-IV/WAIS-IV* Wechsler Intelligence Scale for Children-Fourth Edition/Wechsler Adult Intelligence Scale-Fourth Edition, *WIAT-II* Wechsler Individual Achievement Test-Second Edition, *CMS/WMS* Children's Memory Scale/Wechsler Memory Scale, *VCI* Verbal Comprehension, *PRI* Perceptual Reasoning, *WM* Working Memory, *PSI* Processing Speed, *FSIQ* Full Scale IQ, *NO* Numerical Operations, *GMI* General Memory

* $p < 0.05$

** $p < 0.005$

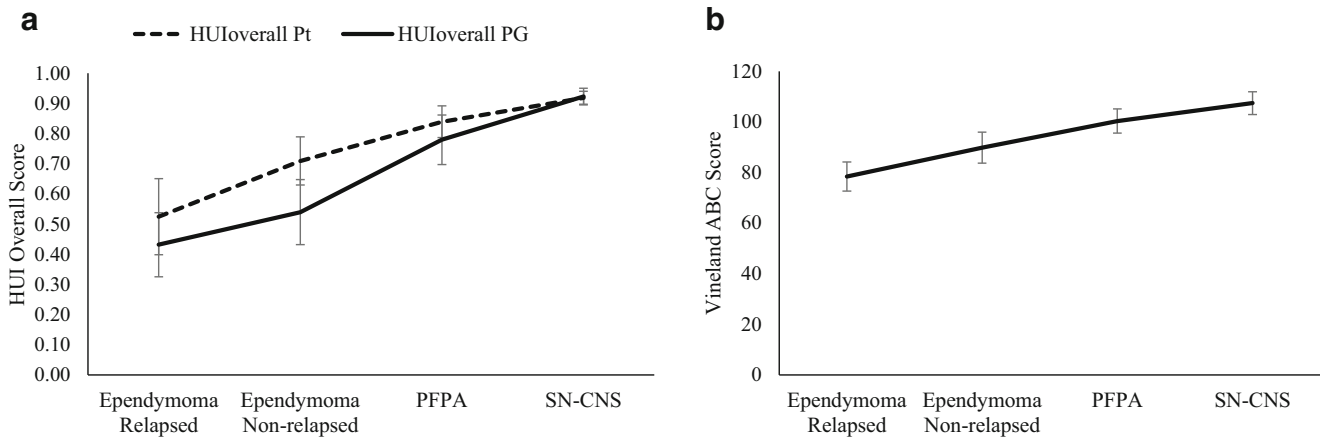

Fig. 1 **a** Mean overall score on the HUI Participant rated (Pt) and Parent/Guardian (PG) rated versions. **b** Mean scores for the Vineland II-Adaptive Behaviour Composite by group. Note: Error bars depict standard error of mean

While significant differences did not exist between the relapsed and non-relapsed ependymoma groups on secondary outcome measures of quality of survival, only the relapsed group demonstrated significantly poorer outcomes on these measures compared to controls. Results suggest that the impact of relapsed ependymoma and subsequent CNS radiotherapy has a significant detrimental impact on children's quality of survival and these difficulties persist over time.

Significant differences existed between non-relapsed and relapsed ependymoma groups on the following measures: Perceptual Reasoning, Full Scale IQ, Word Reading and Numerical Operations, where the non-relapsed group consistently performed better. Direct comparison between those who relapsed and were subsequently irradiated compared to those who did not require radiotherapy suggests that significant detriment to intellectual development, academic achievement and memory is sustained if the brain is irradiated compared to individuals with the same diagnosis that had received multiagent chemotherapy only.

Significant differences were observed to a lesser extent between the other groups. The ependymoma group differed from SN-CNS controls on Processing Speed and General Memory, and control groups differed significantly from each other on Numerical Operations. The most marked differences in scores existed between the ependymoma relapsed group relative to all other groups. As the non-relapsed ependymoma group only differ from controls on two measures, this suggests their scores are more often similar to those of the control groups than individuals who have the same diagnosis but have had disease progression and subsequent radiotherapy. Group averages in Table 2 demonstrate an improving neurocognitive trend dependant on diagnoses and treatment, in line with stated hypotheses. Therefore, the results suggest that improved long-term neurocognitive outcomes are achieved in individuals where cranial radiotherapy is avoided.

Primary outcome comparisons between each group and population norms demonstrated no significant differences between scores in SN-CNS controls. This suggests that the SN-CNS group who have not received any craniospinal adjuvant therapies have neurocognitive function concordant with the general paediatric population. All other groups had some significant differences from population norms. The relapsed ependymoma group differed significantly from normative data on all primary measures. In contrast, the non-relapsed ependymoma group differed significantly on Processing Speed and the PFPA group differed significantly from population norms on Processing Speed and Numerical Operations.

While the ependymoma relapsed group demonstrated more profound deviations from the general paediatric population, these findings indicate that children diagnosed with a brain tumour as well as receiving an intervention, be it neurosurgery alone or with adjuvant therapies following this surgery, perform at a lower level of cognition compared to the general population over 10 years post diagnosis. Given concerns for 'growing into deficit' [18] and the 'double hazard' model [19] indicating younger children have a greater vulnerability for significant residual cognitive impairment and the presented data, the need for long-term prospective neurocognitive surveillance and improved access to paediatric neurorehabilitation services is critical. It highlights the need for the use of standardised neurocognitive batteries [16, 17] to permit accurate long-term neurocognitive characterisation.

Previous literature reports progression free survival is higher in individuals who have received craniospinal radiotherapy at any age; however, these reports tend to be estimates or medians and do not reflect true data [13]. Merchant et al. [13] reported follow-up data on 'more than half the cohort' 24 months post initiation of radiotherapy. The values stated explicitly in that paper were the mean FSIQs of 89.7 ± 2.8 (< 36 months old) vs. 98.7 ± 3.1 (> 36 months old). From the mean Full Scale IQ data

Table 5 One-sample *t* tests comparing primary outcomes of all groups to population norms (test value = 100)

Group	Measures	df	*t*	*p*	Mean difference	95% CI for mean difference	
						Upper	Lower
Ependymoma relapsed	VCI	12	− 7.13	.000*	− 32.00	− 22.22	− 41.78
	PRI	12	− 5.41	.000*	− 28.31	− 16.90	− 39.71
	WM	12	− 7.10	.000*	− 26.92	− 18.66	− 35.19
	PSI	12	− 8.02	.000*	− 34.77	− 25.32	− 44.22
	FSIQ	12	− 7.92	.000*	− 37.38	− 27.10	− 47.67
	WR	12	− 6.34	.000*	− 36.69	− 24.08	− 49.31
	Spelling	11	− 5.19	.000*	− 27.92	− 16.07	− 39.77
	Numerical Operations	11	− 4.85	.001*	− 31.83	− 17.37	− 46.29
	General Memory	10	− 7.27	.000*	− 31.55	− 21.88	− 41.21
Ependymoma non-relapsed	VCI	15	− 2.98	.009	− 16.38	− 4.67	− 28.08
	PRI	15	− 2.17	.046	− 11.06	− .20	− 21.93
	WM	15	− 3.33	.005	− 16.31	− 5.88	− 26.74
	PSI	15	− 4.49	.000*	− 20.13	− 10.57	− 29.68
	FSIQ	15	− 3.48	.003	− 19.13	− 7.40	− 30.85
	Word Reading	15	− 2.36	.032	− 13.56	− 1.33	− 25.79
	Spelling	15	− 2.05	.059	− 11.50	.48	− 23.48
	Numerical Operations	14	− 2.16	.049	− 12.27	− .07	− 24.46
	General Memory	15	− 2.04	.059	− 13.50	.61	− 27.61
PFPA	VCI	14	− 2.71	.017	− 9.47	− 1.98	− 16.95
	PRI	14	− 2.36	.033	− 9.53	− .87	− 18.20
	WM	14	− 2.66	.019	− 11.27	− 2.18	− 20.36
	PSI	14	− 4.54	.000*	− 13.93	− 7.36	− 20.51
	FSIQ	14	− 3.33	.005	− 13.07	− 4.66	− 21.47
	Word Reading	14	− 1.45	.169	− 8.13	3.89	− 20.16
	Spelling	14	− 2.53	.024	− 12.87	− 1.94	− 23.79
	Numerical Operations	14	− 4.16	.001*	− 18.53	− 8.99	− 28.08
	General Memory	14	− 1.02	.326	− 2.93	3.24	− 9.11
SN-CNS	VCI	14	− .96	.352	− 2.87	3.52	− 9.26
	PRI	14	− .21	.838	− .60	5.56	− 6.76
	WM	14	−.87	.401	− 4.00	5.56	− 13.90
	PSI	14	− 1.38	.188	− 5.40	2.97	− 13.77
	FSIQ	14	− 1.45	.171	− 3.93	1.91	− 9.77
	Word Reading	14	.04	.968	.13	7.03	− 6.77
	Spelling	14	− .03	.974	− .13	8.58	− 8.84
	Numerical Operations	14	.43	.671	1.40	8.31	− 5.51
	General Memory	14	2.33	.035	9.07	17.41	.73

df degrees of freedom, *CI* confidence interval, *VCI* Verbal Comprehension, *PRI* Perceptual Organisation, *WM* Working Memory, *PSI* Processing Speed, *FSIQ* Full Scale IQ. Asterisks indicate significant differences when Bonferroni correction applied

shown in Table 2, it is clear that the results obtained from the current study are markedly different; not only do relapsed ependymoma and non-relapsed ependymoma groups have much lower mean Full Scale IQ scores (62.62 and 80.88, respectively), but the PFPA group who received neurosurgery only also had a lower mean Full Scale IQ (86.93) score than previously reported in Merchant et al.'s study. Massimino et al. [11] reported neurocognitive data on a limited number of individuals which they stated were inconclusive. They reported five Full Scale IQ scores: three for patients with ependymoma who had avoided radiotherapy (65, 112 and 82), and two from patients with ependymoma who had undergone radiotherapy (40 and 44). Although small, these findings are more consistent with the results from the present study than those reported in Merchant et al.

A limitation of the present study was cross-sectional methodology restricting the interpretation of results as group differences may not necessarily have reflected changes relevant to the diagnosis or treatments [20]. Small sample sizes were used due to low recruitment rates. However, given the need to develop treatments that confer the least morbidity, it is concerning that this is to date the only paper to report UK multi-centre neurocognitive outcomes of children diagnosed with brain tumours.

It is acknowledged that differences between participants in the number of surgical resections and type/dose of radiotherapy administered may have an impact on neurocognitive outcomes. It is also noted that there is evidence for detriment to neurocognitive function following treatment with chemotherapy, particularly so for those with methotrexate induced leukoencephalopathy [21]. Quality of survival and health status has also been reported to be significantly lower in populations diagnosed with medulloblastoma who received chemotherapy following craniospinal irradiation compared to those patients who received radiotherapy alone, at follow-up 7 years post diagnosis [22]. A limitation of the current study is that the effects of radiotherapy cannot be adequately isolated from those of chemotherapy and neurosurgery. Equally, it is not possible to disaggregate the impact of relapse itself from the effects of treatment, when determining whether an association exists between radiotherapy and poorer outcomes. Regardless of the cause of neurocognitive deficits observed, there is growing literature on significant adverse outcomes during long-term survivorship of childhood brain tumours.

This multi-centre long-term follow-up study is the first of its kind from the UK and has compared neurocognitive outcomes of 59 tumour survivors with various diagnoses and treatments. Findings indicate that administering cranial irradiation for relapsed ependymoma has very significant late cognitive effects when assessed at an average of 10 years post diagnosis and suggests that avoiding radiotherapy in children ≤ 3 years old who did not relapse has helped preserve neurocognitive function. Long-term follow-up of similar treatment protocols is recommended to gain an accurate understanding of the quality of survival for long-term survivors of ependymoma, who did or did not receive radiation at an age when the brain is structurally and functionally immature. Presented data will enable eventual comparison with results from the current on-going SIOP Ependymoma II trial which ensures neurocognitive, learning and quality of survival outcomes are collected at agreed time points thus permitting analyses that will determine whether or not neurocognitive outcomes will be improved upon further.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee at which the studies were conducted. Ethical approval was awarded by the National Research Ethical Service (08/H1311/92).

Informed consent Informed consent was obtained from all parents/guardians of participants, along with each participant providing informed assent.

Conflict of interest The authors declare that there are no conflicts of interest.

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