Child's Nervous System (2019) 35:2327–2338
https://doi.org/10.1007/s00381-019-04402-x

ORIGINAL ARTICLE

Childhood medulloblastoma—a single institution's historical perspective on survival and functional morbidity

Kim Phipps[1] · Matthew A. Kirkman[1,2] · Kristian Aquilina[1] · Mark Gaze[3,4] · Antony Michalski[3] · Angie Wade[5] · Richard Hayward[1]

Received: 16 May 2019 / Accepted: 27 September 2019 / Published online: 4 November 2019

Abstract

Purpose To compare results from a third (1995–2010) cohort of children with medulloblastoma with two previous series (J Neurosurg 86:13–21, 1997; Arch Dis Child 54:200–203, 1979) to analyse the effects of management changes aimed at improving both overall and event-free survivals (OS and EFS) and functional outcomes.

Methods Review of neuro-oncology and imaging databases and previously published results.

Results There was no statistically significant improvement in the 5-year OS for 104 children diagnosed 1995–2010, 61.5% (95% CI, 52.9, 71.6), compared with 50% of the 80 children presenting 1980–1990 (J Neurosurg 86:13–21, 1997) (difference 11.5%; 95% CI, 2.8, 25.4). Five-year OS for 96 children suitable for risk-stratification was overall 66% (95% CI, 57.9, 75.8); standard risk 77.8% (95% CI, 67.4, 89.7); high risk < 3 years 50.0% (95% CI, 32.3, 77.5); high risk ≥ 3 years 54.5% (95% CI, 37.2, 79.9); 5-year EFS were standard risk 68.5% (95% CI, 57.2, 82.1); high risk < 3 years 40.0% (95% CI, 23.4, 68.4); and high risk ≥ 3 years 36.4% (95% CI, 20.9, 63.2); overall 55.2% (95% CI, 46.1, 66.1). Of 62/63 ≥ 5-year survivor, 9 died later from tumour relapse and 4 from second malignancy. Functional outcomes of 62 of the 63 ≥ 5-year survivors: 67.7% had educational issues requiring remedial input; 18% restricted mobility indoors and outdoors; 59.7% hearing impairment (42% prescribed aids).

Previous presentation
Papers based on this study have been presented at:
• The 17th International symposium on Pediatric Neuro-Oncology, Liverpool, UK. June 2016
• The 45th annual meeting of the International Society for Pediatric Neurosurgery, Denver, CO, USA, October 2017

✉ Richard Hayward
Richard.hayward@gosh.nhs.uk; Richard.d.hayward@gmail.com

Kim Phipps
Kim.phipps@gosh.nhs.uk

Matthew A. Kirkman
Matthew.kirkman@gmail.com

Kristian Aquilina
Kristian.aqualina@gosh.nhs.uk

Mark Gaze
mgaze@nhs.net

Antony Michalski
Antony.michalski@gosh.nhs.uk

Angie Wade
a.wade@ucl.ac.uk

[1] Department of Neurosurgery, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC2N 3JH, UK

[2] Victor Horsley Department of Neurosurgery, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

[3] Department of Haematology and Oncology, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC2N 3JH, UK

[4] Department of Oncology, University College London Hospitals NHS Foundation Trust, 250 Euston Road, London NW1 2PG, UK

[5] Population, Policy and Practice Programme, Great Ormond Street Institute of Child Health, UCL, 30 Guilford Street, London WC1N 1EH, UK

Conclusions

1. Comparison of this single-institution series with its predecessor found that revised chemotherapy and RT protocols and greater accuracy of risk stratification did not result in statistically significant improvements in either survival or treatment-related functional disability.
2. Extended (> 5-year) follow-up is essential if 20% of late deaths from relapse and second malignancies are not to be overlooked.

Keywords Medulloblastoma · Radiotherapy · Neurosurgery, · Chemotherapy, · Functional outcome

Introduction

The dramatic improvement in 5-year overall survival (OS) between the first and second halves of a first (1965–1974) series of unselected children with medulloblastoma treated at our institution [1] could be attributed to improved radiotherapy (RT) techniques. There was then no statistically significant difference in 5-year OS between the second half (1970–1974) of that series and our 1980–1990 [2] series (50% and 41%, respectively).

Subsequent management changes introduced to reduce morbidity without compromising survival include routine chemotherapy for standard-risk children [3] (with reduced craniospinal radiotherapy (CS-RT) dosages); MR imaging and CSF cytology for more accurate clinical staging; advances in CS-RT (MRI-fused, CT planned, intensity-modulated radiotherapy); and exclusion of such high-risk embryonal tumours as atypical teratoid rhabdoid tumours (ATRT) that would have 'contaminated' earlier series.

The purposes of this study were (i) to investigate the effect of these changes on a series of children diagnosed immediately prior to the era of treatment protocols determined by the molecular genetic profiling of individual tumours and (ii) to provide a long-term perspective on the progress of medulloblastoma management against which the results of such contemporary series can be judged.

Methods

A retrospective review of clinical records contemporaneously completed neuro-oncology databases and imaging of all patients diagnosed with medulloblastoma between May 1995 and May 2010 as well as published results from our previous series [1, 2].

To calculate a Chang-derived 'M' score[4, 5], all patients underwent spinal MRI as part of initial staging; residual tumour was assessed by MRI 24–48 h following posterior fossa surgery[6] (Table 1); and lumbar puncture for CSF cytology was performed 14 days post-tumour surgery (Table 1).

The analysis of surgical complications was restricted to two with recognised potential for long-term morbidity: posterior fossa syndrome (PFS) [7, 8] and deep wound (including CSF) infection (DWI).

Tumours were classified histologically according to 1995–2010 nomenclature: *Medulloblastoma* and *Desmoplastic/nodular* or *Anaplastic* subtypes.

Patients were risk-stratified according to 1995–2010 practice:

1. Standard risk≥ 3 years, all tumour subtypes, no metastatic disease on MRI scans, negative CSF cytology (M_0), and < 1.5-cm^2 residual tumour.
2. High-risk

(a)< 3 years at diagnosis

(b)≥ 3 years at diagnosis with metastases on neuroimaging and/or positive CSF cytology (M_1–M_4) and/or > 1.5-cm^2 residual tumour.

Adjuvant therapy

Chemotherapy

Protocols during the study period included:

High risk < 3 years: CCLG (UK Children's Cancer and Leukaemia Group) Infant PNET protocol[1].

High risk ≥ 3 years: CCLG HART 2001 [9, 10]. After closure of this study, families offered the Milan strategy [11].

Standard risk: SIOP PNET3 [12] and SIOP PNET4 [13]–or 'Packer' [3] when no open study available.

Radiotherapy

Craniospinal radiotherapy (CS-RT): linear accelerator megavoltage photons with fractionation protocols according to clinical trials referenced above. Outside trials, whole-CNS treated to 23.4 Gy in M_0 patients (increased to 36 Gy with M_1, M_2, or M_3 disease and/or those not receiving chemotherapy) followed by posterior fossa boost to 54 Gy total (1.8 Gy per fraction in both phases). Patients with M_2 or M_3 disease: a discretionary boost to sites of metastases. Children < 3 years

[1] Surgery → induction (6 cycles every 14 days with G-CSF-induced blood harvest and re-infusion: cyclophosphamide; carboplatin AUC 6.63;vincristine) → Tumour response → involved field(s) RT (max 2 sites) → consolidation therapy (4 cycles cisplatin, vincristine, and lomustine) → No response/progression (and/or close to 3 years) → age adapted CS RT with appropriate boosts to bulk disease

Table 1 Presentation and management details of 96 children available for risk stratification

	Standard risk *n* (%)	High risk (< 3 years) *n* (%)	High risk (≥ 3 years) *n* (%)	All cases *n* (%)
Total number of cases, *n* (%)	54 (56.3)	20 (20.8)	22 (22.9)	96 (100)
Tumour staging (M score), *n* (%)				
• M_0 (no metastatic spread)	54 (100)	13 (65.0)	0	67 (69.7)
• M_1 (metastatic tumour cells seen in CSF only)	0	1 (5.0)	2 (9.1)	3 (3.1)
• M_2 (spread within the brain)	0	1 (5.0)	5 (22.7)	6 (6.3)
• M_3 (spinal spread (± other spread))	0	3 (15.0)	14 (63.4)	17 (17.7)
• M_4 (spread outside CNS)	0	2 (10.0)	1 (4.5)	3 (3.1)
Tumour pathology				
• 'Medulloblastoma'	41 (75.9)	12 (60)	18(81.8)	71 (74)
• Desmoplastic	9 (16.7)	6 (30.0)	0	15 (15.6)
• Anaplastic	4 (7.4)	2 (10.0)	4 (18.2)	10 (10.4)
Surgical complications				
• PFS	13 (24.1)	2 (10.0)	9 (40.9)	24 (25.0)
• DWI	5 (9.3)	2 (10.0)	2 (9.1)	9 (9.4)
• Both	1 (1.9)	1 (5.0)	0	2 (2.1)
Extent of tumour resection				
• GTR (no residual tumour)	42 (77.8)	12 (60.0)	7 (31.8)	61 (63.5)
• NTR (< 1.5-cm^2 residual tumour)	6 (11.1)	6 (30.0)	7 (31.8)	19 (19.8)
• STR (> 1.5-cm^2 residual tumour)	6 (11.1)	2 (10.0)	8 (36.4)	16 (16.7)
CSF diversion required, *n* (%)	9 (16.7)	9 (45.0)	11 (50.0)	29 (30.2)
Adjuvant therapy, *n* (%)				
• Chemotherapy alone	0	2 (10.0)	0	2 (2.1)
• Radiotherapy alone	16 (29.6)	1 (5.0)	2 (9.1)	19 (19.8)
• Chemotherapy and radiotherapy	38 (70.4)	17 (85.0)	20 (90.9)	75 (78.1)

All percentages are calculated with the total number of patients for that risk group as the denominator (except for the last column, where percentages are calculated with all 96 patients in this analysis as the denominator)

CSF, cerebrospinal fluid; *DWI*, deep wound infection; *PFS*, posterior fossa syndrome

without tumour spread received posterior fossa RT (whole CNS irradiation with posterior fossa boost offered to those approaching 3 years with metastatic disease).

To investigate any association between CS-RT timing and OS and EFS, risk-stratified children not scheduled to receive pre-CS-RT chemotherapy were subdivided:

- Commenced CS-RT as initial adjuvant therapy within 6 weeks of tumour surgery, with or without later chemotherapy.
- Commenced CS-RT as initial adjuvant therapy later than 6 weeks of tumour surgery, with or without later chemotherapy.

Functional outcome

Functional outcome was assessed at 5 years post-diagnosis. Details (Table 2) were taken from the records of the unit's neuroendocrine/late effects clinic; from neuropsychology assessments; and, when applicable, trial data forms.

Statistical analysis

All data were analysed using SPSS Statistics version 24.0 (IBM, Armonk, NY, USA). Chi-square tests, or Fisher exact tests where numbers were small or percentages extreme, were used to compare tumour characteristics, management, and outcomes between risk groups. Cox proportional hazard regressions were used to determine associations with overall (OS) and event-free survival (EFS) post-diagnosis (effective date of surgery), pre- and post-adjustment for risk categories. Kaplan-Meier survival plots and model coefficients (hazard ratios (HR)) presented with 95% confidence intervals. Symptom duration was logged prior to inclusion in the models.

For these analyses, EFS was taken from the date of surgery to death, tumour recurrence, or the diagnosis of a second

Table 2 Functional outcome details and results from a group of 62 survivors at 5 years following diagnosis

Domain	Outcome	Number of patients (%)
School	• Normal school—no concerns	20 (32.3)
	• Normal school with some learning concerns—IEP (individual educational plan) in place	10 (16.1)
	• Normal school—with statement of educational needs (in place or applied for) or specialist school for non-cognitive affecting disability such as sight or hearing	24 (38.7)
	• Special school for children with learning difficulties	8 (12.9)
Mobility	• No impairment	21 (33.9)
	• Minor impairment—no restrictions on activities indoors or outdoors	30 (48.4)
	• Impairment sufficient to restrict outdoor activities	8 (12.9)
	• Impairment sufficient to restrict activities both indoors & outdoors (± aids required, e.g. wheelchair)	3 (4.8)
Hearing	• No issues	25 (40.3)
	• Some impairment—no hearing aids required	11 (17.7)
	• Hearing aids required	26 (41.9)
Endocrine	• Growth hormone (GH) replacement not required	13 (21.0)
	• GH replacement prescribed	49 (79.0)

malignancy (whichever occurred first). For all analyses, a P value of < 0.05 was considered statistically significant.

Results

One hundred seventeen children were diagnosed with medulloblastoma between 1995 and 2010. Thirteen referred from overseas with limited UK follow-up data were excluded from further study.

Demographics and presentation

Of the remaining 104 children, 70.2% were male; median age at diagnosis is 6.5 years (range, 19 days–14.9 years); and median duration of symptoms 30 days (range, 1–365). For further details, see Table 3.

OS and EFS

The 30-day mortality for these 104 children was 4.8% (5 patients).

OS at 5 and 10 years was 61.5% and 50.7%, respectively. EFS was 51.0% and 43.3%, respectively.

For further details, see Table 4.

Stratification by risk group

Eight (7.7%) of the 104 children were not risk-stratified:

3 Presented moribund

2 Had pre-existing medical comorbidities (Fanconi's anaemia and ataxia telangiectasia) precluding treatment with standard protocols

1 Intraoperative death

1Poor clinical status made further treatment post-surgery inappropriate

1Clinical deterioration and death at 32 days post-surgery due to rapid tumour growth

The remaining 96 children were stratified as:

1. Standard risk (54)
2. High risk: (42)

(a) < 3 years age at presentation (20)
(b) ≥ 3 years age at presentation (22)

Results for risk-stratified children

Table 5 shows M scores, tumour pathology, extent of tumour removal, need for CSF diversion, surgical complications, and adjuvant therapies.

Proportions of pathological subtypes between risk groups ($p = 0.070$) was not significantly different.

The highest rate of GTR of 77.8% (95% CI 65.1, 86.8) was achieved for standard-risk children, followed by high risk < 3 years 60% (95% CI 38.7, 78.1) and high risk ≥ 3 years 31.8% (95% CI 16.4, 52.7).

The incidence of surgical complications (PFS and DWI) was not significantly different between risk groups. The incidence of PFS in the ≥ 3-year high-risk group (40.9%) was higher than for the < 3-year high-risk (10%) and standard-risk (24.1%) groups.

Table 3 Overview of 104 patients with sufficient data for analysis

Number	104 (of 117 total admissions)
Male gender, *n* (%)	73 (70.2)
Median age at diagnosis in years, *n* (range)	6.5 (19 days–14.9 years)
Median duration of symptoms	30 (1–365 days)
Ethnicity, *n* (%)	
• White/European	55 (52.9)
• Asian	13 (12.5)
• Afro-Caribbean	11 (10.6)
• Middle Eastern	10 (9.6)
• Mixed race	8 (7.7)
• Mediterranean	7 (6.7)
Symptoms of raised ICP, *n* (%)	84 (80.8)
Ataxia, *n* (%)	69 (66.3)
Ophthalmic symptoms, *n* (%)	50 (48.1)

ICP, intracranial pressure

CSF diversion was statistically more likely in the two high-risk categories (45% and 50%, respectively), compared with standard risk (16.7%).

Adjuvant treatment

All 96 risk-stratified patients received adjuvant therapy post-tumour surgery (Table 5).

78/96 patients received chemotherapy alone or in combination with RT. Protocols included 'Packer' [3] (*n* = 36), CCLG Infant PNET (*n* =18), SIOP PNET 3 [12] (1992–2000; *n* = 10), SIOP PNET 4 [13] (20012006; *n* = 7), HART [9] (2001; *n* = 3), Milan [11] (*n* = 2), and COG A9961 [14] (*n* = 1).

One patient received vincristine during RT but died before further chemotherapy.

Six children (6.3%) received no RT:

5Death prior to commencement

1Family refusal

OS and EFS by risk group

For OS and EFS for all 96 children (A and B) and by risk group (C and D), see Fig. 1.

Table 4 Thirty-day mortality and OS and EFS for 104 children

30-day mortality	5 (4.8)
Overall survival, % (95% CI)	
• At 5 years	61.5 (52.9,71.6)
• At 10 years	50.7 (41.5, 61.9)
Event-free survival,% (95% CI)	
• At 5 years	51.0 (42.2–61.5)
• At 10 years	43.3 (33.6, 53.0)

CI, confidence interval

Compared with children with standard risk, OS was significantly lower in high risk < 3 years (hazard ratio (HR), 2.13; 95% CI, 1.04, 4.35; $p = 0.038$). HR was raised for high risk ≥ 3 years at presentation compared with standard risk but failed to attain statistical significance (HR, 1.73; 95% CI 0.85, 3.54; $p = 0.132$). Figure 1 c shows similarity between high-risk subgroup trajectories. EFS was significantly lower in both high-risk groups (< 3 years HR, 2.29; 95% CI 1.18, 4.45; $p = 0.014$; ≥ 3 years HR, 2.26; 95% CI, 1.18, 4.32; $p = 0.014$) compared with standard risk.

Tumour type and survival

All 15 children with desmoplastic/nodular tumours were alive at median follow-up of 9.8 years (range 5.2–16). 7/10 with anaplastic tumours died (median survival 1.3 years; range, 0.4–5.1) while 3 survived (median follow-up 5.2 years; range, 5.2–9.5).

Thirty-eight of remaining 71 children with *Medulloblastoma* died (median survival 2.7 years; range, 0.25–18.3), 10/12 (83%) diagnosed < 3 years and 28/59 (47%) diagnosed > 3 years ($p = 0.02$).

Median follow-up of 33 survivors (46.5%) was 9.5 years (range, 5–18.5).

Risk group adjusted OS and EFS of all 96 risk-stratified children (Table 6)

A Cox regression analysis investigated these co-variables: age at diagnosis, gender, ethnicity, symptom duration prior to presentation, tumour (M) staging, medulloblastoma subtype, extent of tumour resection, CSF diversion, surgical complications, and adjuvant therapy. Models were repeated adjusting for risk group.

Table 5 Outcomes of 96 patients according to risk group

	Standard risk (%)	High risk (< 3 years) (%)	High risk (≥ 3 years) (%)	All cases (%)
Total number of cases, n (%)	54 (56.3)	20 (20.8)	22 (22.9)	96
Overall survival, % (95% CI)				
• At 5 years	77.8 (67.4, 89.7)	50.0 (32.3, 77.5)	54.5 (37.2,79.9)	66.7(57.9, 75.8)
• At 10 years	63.9 (51.5, 79.3)	43.7 (26.3, 72.9)	Not estimable	54.9 (45.3, 66.5)
Event-free survival, % (95% CI)				
• At 5 years	68.5 (57.2,	40.0 (23.4, 68.4)	36.4 (20.9, 63.2)	55.2(46.1, 66.1)
• At 10 years	52.2 (39.1, 69.7)	34.3 (18.5, 63.5)	Not estimable	43.8 (34.3, 55.8)
Incidence of 2nd malignancies, *n* (%)				
• GBM	1 (1.8)	1 (5.0)	0	2 (2.1)
• DIPG	1 (1.8)	0	0	1 (1.0)
• Ossifying sarcoma	0	1 (5.0)	0	1 (1.0)
• Thyroid carcinoma	1 (1.8)	0	0	1 (1.0)
• Myelodysplastic syndrome	0	1 (5.0)	0	1 (1.0)
Incidence of late deaths[a]				
• Medulloblastoma relapse	7 (12.7)	0	2 (9.5)	9 (9.4)
• Second malignancy (see above)	2 (3.6)	2 (10.0)	0	4 (4.2)

All percentages calculated with the total number of patients for that risk group as the denominator (except for the last column, where percentages are calculated with all 96 patients in this analysis as the denominator)

DIPG, diffuse intrinsic pontine glioma; *GBM*, glioblastoma multiforme

[a] Defined as occurring more than 5 years following diagnosis

Because of small numbers, certain subgroups were combined:

Ethnicity: White/European against the remainder of the cohort.

Tumour staging: M_0 against $M_{1–3}$.

Adjuvant therapy: Those receiving chemotherapy against those not.

OS was significantly reduced for those with a shorter symptom duration with and without adjustment for risk group, anaplastic subtype when adjusting for risk group (although similar when unadjusted), and approached significance in the absence of surgical complications whether adjusted or not for risk group. With and without adjustment for risk group, shorter EFS was significantly associated with shorter symptom duration and anaplastic subtype, and approached significance for those with tumour stage $M_{1–3}$, when unadjusted.

Timing of adjuvant radiotherapy

There was no significant difference in OS or EFS between children starting CS-RT within 6 weeks of diagnosis (42 of 67 children eligible for an under 6-week start) and those with a later than 6-week start (15), whether adjusted for risk group or not (Table 6).

Late deaths

Sixty-three children survived ≥ 5 years post-diagnosis of whom 13 (13.5%) subsequently died:

9 Seven standard risk and 2 high risk (≥ 3 years) from relapse of medulloblastoma (median 7.9 years (range 5.2–18.3) post-diagnosis

4 Two standard risk and 2 high risk (< 3 years) from second malignancy (see below).

There was no significant difference in proportion of late deaths between risk groups (95% CI) or between standard and both high-risk groups—16% (9, 28), 10% (3, 30), and 10% (3, 29) respectively (Fisher's exact test $p = 0.775$).

Second malignancies

Six children developed a second malignancy at median 7.5 years (range 2.6–13.2) post-diagnosis (Table 5). All six had had RT and five chemotherapy. Four died at a median of 9.65 years (range 8.5–13.8). Two with thyroid carcinoma and myelodysplastic syndrome were alive at 16.6 and 9.3 years, respectively.

There was no significant difference in rates of second malignancy between risk groups (Fisher's exact test $p = 0.130$).

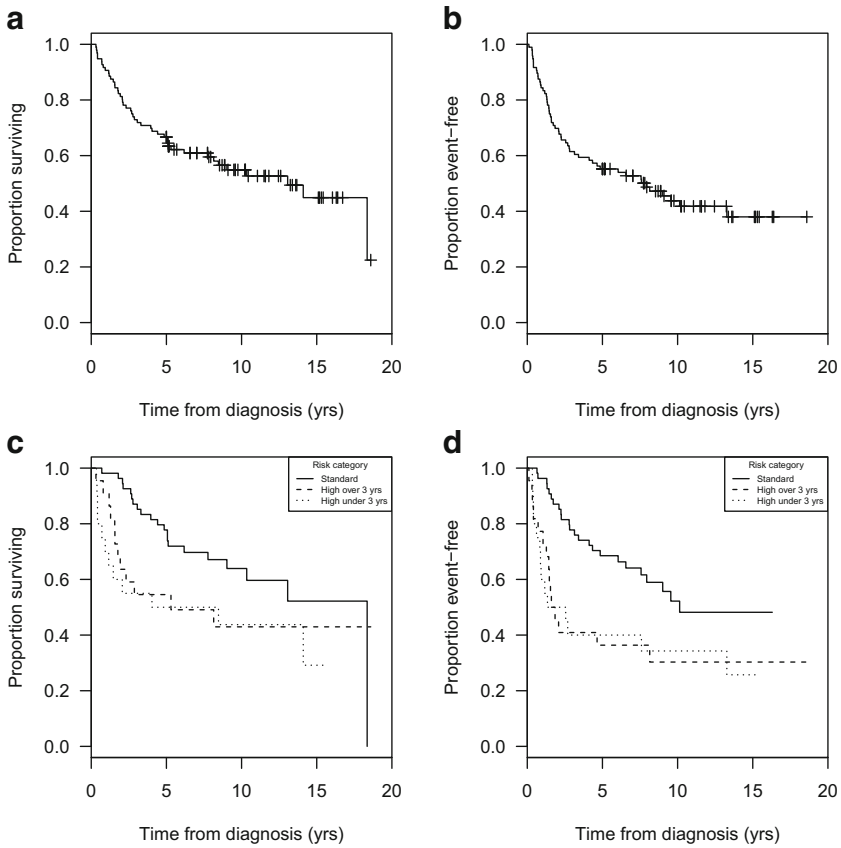

Fig. 1 Kaplan-Meier survival curves showing **a** overall survival and **b** event-free survival for the 96 patient cohort. **c** and **d** show OS and EFS within risk groups for these 96 patients

Functional outcome

Data (Table 2) was available for 62 of 63 patients surviving ≥ 5 years post-diagnosis (10/62 diagnosed < 3 years; 42/62 > 3 years).

Prior to onset of their tumour-related symptoms, 58/62 (93.5%) had no functional disability. At their ≥ 5-year assessment, 55 (89%) patients had a degree of functional disability (need for growth hormone replacement excluded):

42/62 (67.7%) Educational issues sufficient to need remedial intervention (6/10 diagnosed < 3 years; 36/52 > 3 years). Of 8/62 (13%) requiring education in special schools, 5 had PFS and 2 had SI

11/62 (18%)Restricted mobility both outdoors and indoors (3/10 diagnosed age < 3 years; 8/52 diagnosed age > 3 years)

10/62 (16%)Combined educational and mobility disability (3/10 diagnosed age < 3 years; 7/52 diagnosed age > 3 years)

37/62 (59.7%) Hearing impairment (26 prescribed aids)

49/62 (79.0%) Prescribed growth hormone (GH)

Overlap within categories of disability was common. 23/62 (37%) had issues in education, mobility, and hearing, while 4/62 had issues affecting only their education, 4/62 issues affecting only their mobility, and 5 affecting only hearing.

To look for possible variations in functional outcome during the study period, results for 33 ≥ 5-year survivors treated 1995–2002 were compared with 29 treated 2003–2010:

- A fall in the need for remedial educational intervention from 57.6% in the first half of the series to 44.8% in the second was not statistically significant (difference 12.7%; 95% CI, 12.9, 38.4; $p = 0.324$).
- There was a highly significant increase in both documented hearing impairment from 11/33 in the first half to 26/29 in the second, 56.3% (95% CI, 35.5, 77.1; $p < 0.0001$), and in prescription of hearing aids from 6/33 to 20/29, 50.8% (95% CI, 28.9, 72.7; $p < 0.0001$).

Discussion

This study failed to show a statistically significant improvement in 5-year OS (61.5%) for 104 children diagnosed with medulloblastoma, unselected by age or condition compared with our 1980–1990 series [2] (50%) of 80 children; difference 11.5%; 95% CI, 2.8, 25.4.

To demonstrate a statistically significant improvement in 5-year OS, it is necessary to compare it with the second cohort in the 1965–1974 series [1] in which 39.3% of 17 children survived (difference 22.3%; 95% CI, 1.6, 40.3) [1]—confirmed by trend analysis over the three periods (Linear-by-Linear Association $p = 0.030$).

Table 6 Event-free and overall survivals with and without adjustment for risk group

Variable	Event-free survival				Overall survival			
	Unadjusted for risk group		Adjusted for risk group		Unadjusted for risk group		Adjusted for risk group	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at diagnosis	0.94 (0.87, 1.02)	0.128	0.99 (0.89, 1.09)	0.785	0.94 (0.86, 1.03)	0.173	0.99 (0.88, 1.11)	0.866
Gender (male vs female)	0.92 (0.51, 1.66)	0.783	1.01 (0.55, 1.83)	0.987	1.13 (0.58, 2.20)	0.721	1.24 (0.63, 2.43)	0.529
Ethnicity								
• White/European vs rest	1.26 (0.73, 2.17)	0.414	1.22 (0.70, 2.11)	0.481	1.35 (0.74, 2.47)	0.326	1.30 (0.71, 2.38)	0.393
Symptom duration (log days)	0.77 (0.60, 0.97)	*0.025*	0.75 (0.59, 0.97)	*0.027*	0.73 (0.57, 0.94)	0.016	0.722 (0.55, 0.94)	0.017
Tumour staging (M score)								
• M_0 vs M_1–M_3[a]	1.76 (1.00, 3.09)	0.051	0.71 (0.22, 2.28)	0.561	1.56 (0.84, 2.89)	0.156	1.03 (0.97, 3.48)	0.957
Pathology								
• Anaplastic vs other medulloblastoma $n = 81$)[b]	**3.75 (1.78, 7.91)**	*< 0.0001*	4.88 (2.24, 10.66)	*< 0.0001*	2.13 (0.94, 4.83)	0.0715	2.44 (1.05, 5.70)	0.038
Extent of tumour resection vs STR								
• GTR	0.64 (0.32, 1.24)	0.185	0.81 (0.40, 1.63)	0.549	0.65 (0.32, 1.33)	0.241	0.75 (0.36, 1.57)	0.440
• NTR	0.86 (0.38, 1.95)	0.716	0.81 (0.35, 1.86)	0.620	0.70 (0.28, 1.75)	0.442	0.64 (0.25, 1.60)	0.339
• GTR + NTR	1.47 (0.79, 2.79)	0.246	1.24 (0.64, 2.42)	0.53	1.51 (0.76, 3.00)	0.242	1.4 (0.70, 2.82)	0.344
CSF diversion	1.64 (0.93, 2.88)	0.085	1.28 (0.70, 2.31)	0.421	1.08 (0.56, 2.07)	0.817	0.82 (0.41, 1.64)	0.580
Surgical complication(s) (PFS and/or DWI)	0.64 (0.36, 1.16)	0.142	0.60 (0.33, 1.11)	0.102	0.53 (0.27, 1.02)	*0.058*	0.52 (0.26, 1.01)	*0.054*
Adjuvant therapy								
• Chemotherapy vs no chemotherapy	1.01 (0.52, 1.97)	0.971	0.67 (0.32, 1.40)	0.288	0.84 (0.42, 1.66)	0.616	0.56 (0.26, 1.21)	0.139
• Under versus over 6-week RT start (42 v. 15 of 67 eligible patients)	1.76 (0.84, 3.71)	0.135	1.67 (0.78, 3.61)	0.188	1.73 (0.79, 3.81)	0.170	1.74(0.78, 3.85)	0.179

CI, Confidence Interval; HR, Hazard Ratio

[a] Owing to the low numbers in all categories except M_0, all M_1–M_3 children (27) have been compared with M_0 (69 children)

[b] Excludes desmoplastic medulloblastoma ($n = 15$) as all this group survived

There was also no statistically significant improvement in 5-year OS for those in the more favourable prognostic groups between this series and our 1980–1990 study [2]—54/96 (77.8%) for standard-risk patients compared with 16/22 (72.7%) with total removals and no metastases at presentation (mean difference 5.1%; 95% CI, 14, 27.8).

Confidence limits are broad however and it is acknowledged that clinical benefit of up to 25% could be 'concealed' within them.

This apparent stalling of survival rates for medulloblastoma is in line with the *2012 Progress Report of the UK National Registry of Childhood Tumours* that recorded (their Table 3.2) improving 5-year survival rates for 1978–1990, 1991–1995, and 1996–2000 cohorts (51 to 66%) but little change for cohorts 2001–2005 and 2006–2010. A later UK-wide analysis [15] reported (their Table 3.1) no significant change in 5-year survival between 2003–2007 and 2008–2012 cohorts (62% and 63%, respectively) while a Canadian multicentre study [16] reported, 'The survival rate increased during the interval of 1996–2000, then remained stable'. A recent US population-based study [17] of 1735 children under 20 years diagnosed with medulloblastoma between 1973 and 2012 reported 'a critical time-point, around 1990, in which there has been a significant improvement in survival'.

These results are despite changes, intended to improve both survival and functional outcomes:

1. Adjuvant therapy

Children aged 2–3 years in our 1980–1990 [2] series were treated with 36-Gy CS-RT. Chemotherapy as first-line treatment was reserved for those < 2 years or with metastatic disease at diagnosis. Over 80% of patients in the present series received chemotherapy. Its combination with reduced dose CS-RT (23.4 v 36 Gy) for standard-risk patients was not associated with a decrease in survival. Although its effect on OS and EFS failed to reach statistical significance whether or not adjusted for risk group, broad confidence limits mean that some improvement of clinical importance cannot be excluded.

Although differences in outlook have been connected with delay in starting radiotherapy [13], we found no statistically significant association for those children over 3 years whose RT commenced within or longer than 6 weeks of their tumour surgery, although once again this may be related to smaller numbers providing insufficient statistical power to detect modest differences.

2. Histological diagnosis

Nine children with posterior fossa ATRT (definitively described in 1996 [18]) were diagnosed during this study period. Assuming no change in incidence, our 1980–1990 series [2] could have been 'contaminated' by 8 such cases, adversely affecting its results while the present study should have benefitted from their exclusion.

3. Advances in imaging

For our 1980–1990 series, intracranial tumour spread was identified by CT and spinal metastases by positive contrast myelography [2]. The superior accuracy of tumour staging by MRI should, by cohort migration (the *Will Rogers Phenomenon* [19]), improve survival for individual risk groups. It should not however affect overall survival unless it led to effective changes in management such as more intensive chemotherapy regimens for high-risk groups.

While statistical significance with 95% confidence intervals remains standard for observational studies, the rarity of medulloblastoma means the numbers a single centre needs for a meaningful assessment of its results may have been recruited over many years and confidence intervals necessarily broad. Single-centre series do however have advantages over multicentre studies that recruit greater numbers over shorter periods including consistency of admission/exclusion criteria, imaging, clinical management, pathology, follow-up, and often personnel.

Although our results are broadly in line with two recent large multicentre series [16, 17], many factors limit direct comparisons:

1. Short-term (< 5 years) series miss late deaths from recurrence or second tumours [14, 20] (here 13/63 or 21% of ≥ 5-year survivors) as well as late cognitive decline [21–23]
2. Entries limited to a particular disease stage—i.e. standard risk [13]
3. Variations in upper and lower recruitment ages. ('Children over 14 years of age had a significantly better overall survival than those age 5–14' while 'Children under the age of 5 years had a significantly lower survival than older children' [16])
4. No independent review of pathology and imaging for multicentre studies
5. Wide variations in exclusion criteria and numbers [13, 14, 16] including early deaths before starting adjuvant therapy (7.7% in the present series)

Late recurrence and the development of second tumours

This study confirms previous reports [13, 14, 20] that although statistical attention may be on 5-year survival, children who have passed that milestone still face a near 21% late attrition due to tumour relapse and the development of second tumours. The US population-based study [17] reported, 'The subset who survive 8 years or longer following initial diagnosis are likely long-term survivors'. The median survival period post-diagnosis for our 9 children succumbing to their medulloblastoma > 5 years post-diagnosis was 7.9 years.

Functional outcomes

Results based on survival alone provide a distorted image until refracted through the lens of treatment-related morbidity.

While functional outcomes in our 1980–1990 [2] series were recorded at ≥ 3 years (40 surviving children) and at > 5 years (25 surviving children) post-diagnosis, for the present study we analysed outcomes for all survivors at 5 years post-diagnosis. Our broad grading of performance levels for education, mobility, and hearing revealed (with need for growth hormone replacement excluded) a high (89%) level of disability with 37% of patients having issues affecting all three modalities.

Although differences in the timing of data collection, changes in social attitudes and increased intensity of follow-up assessments combined with heightened awareness and earlier intervention make direct comparison difficult; there appears to have been no improvement in the incidence of learning disability. Forty-two (68%) of those alive 5 years post-diagnosis in the present series require remedial assistance for their education (including 8 (13%) in special schools) compared with 36% of 56 children

surviving 3 years post-diagnosis in our 1980–1990 series (including 14% in special schools).

A report on the functional morbidity of PNET 3 [23] found a statistically significant ($p < 0.05$) increase in need for both 'Special Education Service' and 'Extra educational help in most recent school year' for those receiving both RT and chemotherapy (38% and 58%, respectively) compared with those treated with radiotherapy only (44% and 62%, respectively). Although it attributed the difference to increased exposure to chemotherapy, this has been disputed [24]. The educational status of patients treated under PNET 4 [13] was not examined separately but 41–48% of parents reported their children had borderline or reduced QOL [25].

It is disappointing therefore that despite standard-risk children in the present series receiving reduced dose CS-RT a high level of educational disability (learning difficulty) persists.

We attribute the significant rise in hearing loss in children treated in the second half of the present series to the increased use of platinum-based chemotherapy with protocol-driven audiological testing of all children. These have led to its early detection with, where appropriate, treatment modifications and early prescription of aids to allow children with hearing impairment to perform effectively in their various educational, social, and physical environments.

Improved recognition of hormonal endocrine deficiencies and protocol-driven attention to late endocrine effects could also explain the rise in children requiring growth hormone replacement from 66% of the 60 children in our 1980–1990 series [2] who underwent formal endocrine assessment to 79.0% in the present series (95% CI, 53–78%).

The future

The 1995–2010 series saw the introduction of molecular genetic profiling of childhood CNS tumours [26] and, in its latter stages, the deployment of treatment protocols based on the results [27]. Knowledge that medulloblastoma is a spatially[28] and genetically heterogeneous tumour that can be divided into distinct genetic sub-groups [29–32] has already increased the accuracy of survival predictions [33, 34] compared with those restricted to clinical, radiological, and histological data. It has also opened the way to molecularly mediated/targeted therapies [35–37], leading to trials of treatment protocols aimed at reducing morbidity without compromising survival. Examples include removing the necessity for GTR [6] and CS-RT reduction for children with low-risk WNT tumours [38] being explored in SIOP PNET 5 [39]; proton beam therapy to reduce the volume of normal tissue irradiated [40, 41]; and immunotherapy [42, 43]. But SIOP PNET 5 is not due to close until 2024, and it will therefore be many years before its results and those from studies of other biologically targeted therapies can be set series such as that presented here to confirm their promise.

The aim of the present study was not to link retrospectively the survival and functional outcome of children with medulloblastoma treated in the period preceding the present genetically modulated era with their tumour's molecular genetic profile. Instead, we have provided a single-centre long-term perspective against which the effectiveness of prospective studies of molecularly determined therapeutic protocols can be judged.

Conclusions

In this single-centre study of 104 children with medulloblastoma ≤ 16 years, unselected by age and condition at presentation, there was no statistically significant increase in overall survival for those treated in 1995–2010 compared with those treated in 1980–1990.

- Treatment-related morbidity remains high.
- Results from studies with ≤ 5-year follow-up should be treated with caution because of late attrition from second malignancies and late recurrence.
- Both multicentre and single-centre studies will be needed if the promise of treatment protocols based on contemporary molecularly stratified therapies is to be confirmed.

Funding information MNG is supported by the National Institute for Health Research, University College London Hospitals Biomedical Research Centre, London, UK.

Compliance with Ethical Standards

Conflict of Interest The authors have declared no conflicts of interest.

References

1. McIntosh N (1979) Medulloblastoma-a changing prognosis? Arch Dis Child 54:200–203. https://doi.org/10.1136/adc.54.3.200
2. David KM, Casey ATH, Hayward RD et al (1997) Medulloblastoma: is the 5-year survival rate improving? J Neurosurg 86:13–21. https://doi.org/10.3171/jns.1997.86.1.0013
3. Packer RJ, Gajjar A, Vezina G et al (2006) Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 24:4202–4208. https://doi.org/10.1200/JCO.2006.06.4980
4. Chang CH, Housepian EM, Herbert C (1969) An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiology 93:1351–1359. https://doi.org/10.1148/93.6.1351
5. Dufour C, Beaugrand A, Pizer B et al (2012) Metastatic medulloblastoma in childhood: Chang's classification revisited. 2012:1–6. https://doi.org/10.1155/2012/245385
6. Thompson EM, Hielscher T, Bouffet E et al (2016) Prognostic value of medulloblastoma extent of resection after accounting for

molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol 17:484–495. https://doi.org/10.1016/S1470-2045(15)00581-1

7. Wells EM, Khademian ZP, Walsh KS et al (2010) Post-operative cerebellar mutism syndrome following treatment of medulloblastoma: neuroradiographic features and origin. J Neurosurg Pediatr 5: 329–334. https://doi.org/10.3171/2009.11.PEDS09131
8. Souweidane M (2010) Posterior fossa syndrome. J Neurosurg Pediatr 5:325–328
9. Taylor RE, Howman AJ, Wheatley K et al (2014) Hyperfractionated accelerated radiotherapy (HART) with maintenance chemotherapy for metastatic (M_{1-3}) medulloblastoma-a safety/feasibility study. Radiother Oncol 111:41–46. https://doi.org/10.1016/j.radonc.2014.01.022
10. Girish Dhall MD, Grodman H, Ji L, Sands S, Gardner S, Dunkel IJ, McCowage GB, Diez B, Allen JC, Gopalan A, Cornelius AS, Termuhlen A et al (2008) Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. Pediatr Blood Cancer 50:1169–1175
11. Gandola L, Massimino M, Cefalo G et al (2009) Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. J Clin Oncol 27:566–571. https://doi.org/10.1200/JCO.2008.18.4176
12. Taylor RE, Bailey CC, Robinson K et al (2003) Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: the International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol 21:1581–1591. https://doi.org/10.1200/JCO.2003.05.116
13. Lannering B, Rutkowski S, Doz F et al (2012) Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: Results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol 30:3187–3193. https://doi.org/10.1200/JCO.2011.39.8719
14. Packer RJ, Zhou T, Holmes E et al (2013) Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. Neuro Oncol 15:97–103. https://doi.org/10.1093/neuonc/nos267
15. Public Health England (2016) Childhood cancer registration in England: 2015 to 2016
16. Johnston DL, Keene D, Kostova M et al (2015) Survival of children with medulloblastoma in Canada diagnosed between 1990 and 2009 inclusive. J Neurooncol 124:247–253. https://doi.org/10.1007/s11060-015-1831-0
17. Weil AG, Wang AC, Westwick HJ et al (2017) Survival in pediatric medulloblastoma: a population-based observational study to improve prognostication. J Neurooncol 132:99–107. https://doi.org/10.1007/s11060-016-2341-4
18. Rourke L. PR and BJ (1996) Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg 85:55–65
19. Feinstein A. SD and WC (1985) The Will Rogers Phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. New Engl Journasl Med 312:1604–1608
20. Ning MS, Perkins SM, Dewees T, Shinohara ET (2015) Evidence of high mortality in long term survivors of childhood medulloblastoma. J Neurooncol 122:321–327. https://doi.org/10.1007/s11060-014-1712-y
21. Ris M, Walsh K, Wallace D, Armstrong FD, Holmes E. Gajjar A. Z and PR (2013) Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961. Pediatr Blood Cancer 60:1350–1357
22. Gudrunardottir T, Lannering B, Remke M et al (2014) Treatment developments and the unfolding of the quality of life discussion in childhood medulloblastoma: a review. Child's Nerv Syst 30:979–990. https://doi.org/10.1007/s00381-014-2388-5
23. Bull KS, Spoudeas HA, Yadegarfar G, Kennedy CR (2007) Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: a follow-up study in PNET 3 trial survivors-on behalf of the CCLG (formerly UKCCSG). J Clin Oncol 25:4239–4245. https://doi.org/10.1200/JCO.2006.08.7684
24. Packer RJ (2008) Reduction of health status 7 years after addition of chemotherapy to cranio-spinal irradiation for medulloblstoma: a follow-up study on PNET-3 trial survivors. Curr Neurol Neurosci Reportsurrent Neurol Neurosci Reports 8:111–113
25. Kennedy C, Bull K, Chevignard M et al (2014) Quality of survival and growth in children and young adults in the PNET4 European controlled trial of hyperfractionated versus conventional radiation therapy for standard-risk medulloblastoma. Int J Radiat Oncol Biol Phys 88:292–300. https://doi.org/10.1016/j.ijrobp.2013.09.046
26. Wood MD, Halfpenny AM, Moore SR (2019) Applications of molecular neuro-oncology-a review of diffuse glioma integrated diagnosis and emerging molecular entities. 1–16
27. Pollack IF, Agnihotri S, Broniscer A (2019) Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr 23:261–273. https://doi.org/10.3171/2018.10.peds18377
28. Morrissy AS, Cavalli FMG, Remke M et al (2017) Spatial heterogeneity in medulloblastoma. Nat Genet 49:780–788. https://doi.org/10.1038/ng.3838
29. Schwalbe EC, Lindsey JC, Nakjang S et al (2017) Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma : a cohort study. Lancet Oncol 18: 958–971. https://doi.org/10.1016/S1470-2045(17)30243-7
30. Taylor MD, Northcott PA, Korshunov A et al (2012) Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123:465–472. https://doi.org/10.1007/s00401-011-0922-z
31. Remke M, Ramaswamy V, Taylor MD (2013) Medulloblastoma molecular dissection: the way toward targeted therapy. Curr Opin Oncol 25:674–681. https://doi.org/10.1097/CCO.0000000000000008
32. Schmidt C (2015) Targeted therapy makes inroads in medulloblastoma. J. Natl. Cancer Inst 107:djv353
33. Bull KS, Kennedy CR, Bailey S et al (2014) Improved health-related quality of life outcomes associated with SHH subgroup medulloblastoma in SIOP-UKCCSG PNET3 trial survivors. Acta Neuropathol. 128:151–153
34. Drezner NL, Packer RJ (2016) The impact of molecular analysis on the survival of children with embryonal tumors. Transl Pediatr 5:5–8. https://doi.org/10.3978/j.issn.2224-4336.2015.11.01
35. Gajjar A, Stewart CF, Ellison DW et al (2013) Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. Clin Cancer Res 19: 6305–6312. https://doi.org/10.1158/1078-0432.CCR-13-1425
36. Kram D, Henderson J, Baig M et al (2018) Embryonal tumors of the central nervous system in children: the era of targeted therapeutics. Bioengineering 5:78. https://doi.org/10.3390/bioengineering5040078
37. Amarante MK, Vitiello GAF, Rosa MH et al (2018) Potential use of CXCL12/CXCR4 and sonic hedgehog pathways as therapeutic targets in medulloblastoma. Acta Oncol (Madr) 57:1134–1142. https://doi.org/10.1080/0284186X.2018.1473635
38. Ellison DW, Onilude OE, Lindsey JC et al (2005) β-catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. J Clin Oncol 23:7951–7957. https://doi.org/10.1200/JCO.2005.01.5479

39. European Clinical Trials database (EUDRACT) www.clinicaltrialsregister.eu/ctr-search/trial/2011-004868-30/AT)
40. Grosshans DR (2016) Proton therapy for paediatric medulloblastoma. Lancet Oncol 17:258–259. https://doi.org/10.1016/S1470-2045(15)00217-X
41. Bernier V, Klein O (2018) Late effects of craniospinal irradiation for medulloblastomas in paediatric patients. Neurochirurgie:6–9. https://doi.org/10.1016/j.neuchi.2018.01.006
42. van Gool SW, Holm S, Rachor J et al (2016) Immunotherapy in atypical teratoid-rhabdoid tumors: data from a survey of the HGG-Immuno Group. Cytotherapy 18:1178–1186. https://doi.org/10.1016/j.jcyt.2016.06.004
43. Mitchell EJS and DA (2017) Immunotherapy for pediatric brain tumors. Brain Sci 7:137