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# Primary postoperative chemotherapy without radiotherapy for treatment of brain tumours other than ependymoma in children under 3 years: Results of the first UKCCSG/SIOP CNS 9204 trial

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ABSTRACT

*Background:* Radiotherapy is an effective adjuvant treatment for brain tumours arising in very young children, but it has the potential to damage the child's developing nervous system at a crucial time – with a resultant reduction in IQ leading to cognitive impairment, associated endocrinopathy and risk of second malignancy. We aimed to assess the role of a primary chemotherapy strategy in avoiding or delaying radiotherapy in children younger than 3 years with malignant brain tumours other than ependymoma, the results of which have already been published.

*Methods:* Ninety-seven children were enrolled between March 1993 and July 2003 and, following diagnostic review, comprised: medulloblastoma ($n = 31$), astrocytoma (26), choroid plexus carcinoma [CPC] (15), CNS PNET (11), atypical teratoid/rhabdoid tumours [AT/RT] (6) and ineligible (6). Following maximal surgical resection, chemotherapy was delivered every 14 d for 1 year or until disease progression. Radiotherapy was withheld in the absence of progression.

*Findings:* Over all diagnostic groups the cumulative progression rate was 80.9% at 5 years while the corresponding need-for-radiotherapy rate for progression was 54.6%, but both rates varied by tumour type. There was no clear relationship between chemotherapy dose intensity and outcome. Patients with medulloblastoma presented as a high-risk group, 83.9% having residual disease and/or metastases at diagnosis. For these patients, outcome was related to histology. The 5-year OS for desmoplastic/nodular medulloblastoma was 52.9% (95% confidence interval (CI): 27.6–73.0) and for classic medulloblastoma 33.3% (CI: 4.6–67.6); the 5-year EFS were 35.3% (CI: 14.5–57.0) and 33.3% (CI: 4.6–67.6), respectively.

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All children with large cell or anaplastic variants of medulloblastoma died within 2 years of diagnosis. The 5-year EFS for non-brainstem high-grade gliomas [HGGs] was 13.0% (CI: 2.2–33.4) and the OS was 30.9% (CI: 11.5–52.8). For CPC the 5-year OS was 26.67% (CI: 8.3–49.6) without RT. This treatment strategy was less effective for AT/RT with 3-year OS of 16.7% (CI: 0.8–51.7) and CNS PNET with 1-year OS of 9.1% (CI: 0.5–33.3).

*Interpretation:* The outcome for very young children with brain tumours is dictated by degree of surgical resection and histological tumour type and underlying biology as an indicator of treatment sensitivity. Overall, the median age at radiotherapy was 3 years and radiotherapy was avoided in 45% of patients. Desmoplastic/nodular sub-type of medulloblastoma has a better prognosis than classic histology, despite traditional adverse clinical features of metastatic disease and incomplete surgical resection. A subgroup with HGG and CPC are long-term survivors without RT. This study highlights the differing therapeutic challenges presented by the malignant brain tumours of early childhood, the importance of surgical approaches and the need to explore individualised brain sparing approaches to the range of malignant brain tumours that present in early childhood.



## 1. Introduction

Young age at diagnosis has long been considered a powerful and adverse prognostic factor for both survival and quality of survival from malignant brain tumours arising in childhood. The reasons are multifactorial, and include ethical considerations of embarking upon high-risk therapies in young and extremely vulnerable infants or toddlers, clinical presentation of a protracted time to diagnosis, acute and delayed toxicities of chemotherapy and cranial and spinal radiotherapy, the latter being particularly high-risk for profound cognitive damage at an early age.[1–3]

The adverse late effects of radiotherapy in young patients reflect the vulnerability of an immature CNS to treatment related damage.[2,4] Whilst the ultimate objective of treatment with chemotherapy might be the avoidance of radiotherapy, pioneering work in the mid 1980s suggested that it was at least possible to delay irradiation by this means.[5,6] Subsequent studies attempted to delay radiotherapy to beyond 3 years of age,[7,8] representing a physiological end-point at which time cell division of the CNS is largely complete in order to preserve cognitive capacity.[9] CNS 9204 was a United Kingdom Children's Cancer Study Group (UKCCSG) and International Society of Paediatric Oncology (SIOP) co-operative trial, initially open to all histopathological sub-types of brain tumour aged less than 3 years. The aims of this study were to improve the duration of survival of very young children with brain tumours by using a chemotherapy strategy aimed at avoiding or delaying radiotherapy. The outcomes of children with ependymoma have already been reported.[10] This paper describes the outcomes of children with other malignant brain tumour types using the same therapeutic approach.

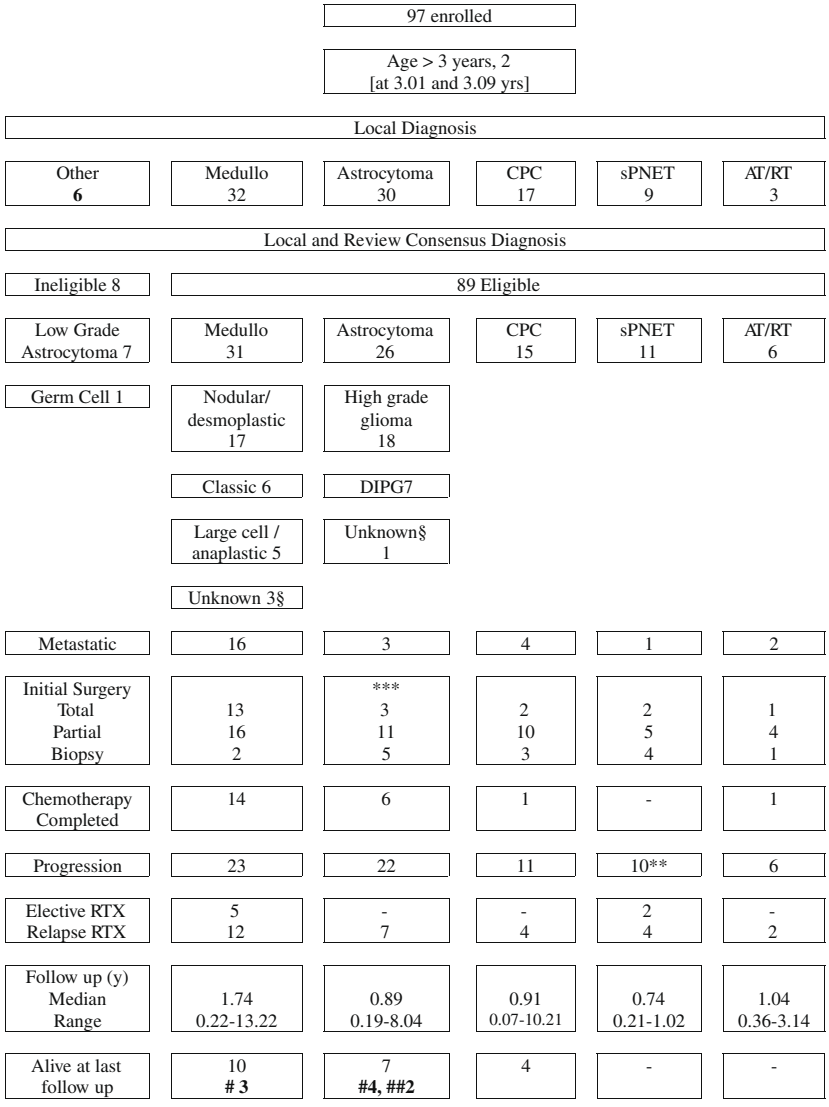
## 2. Methods

### 2.1. Participants

Criteria for recruitment included histological diagnosis of primary intracranial malignant brain tumour or radiological findings consistent with a brainstem astrocytoma, age 3 years or younger at diagnosis and no prior adjuvant drug or radiation therapy. Fig. 1 shows the trial profile. The trial was approved by UKCCSG/SIOP and national ethical approval was obtained. Informed consent was obtained from parents or guardians of each child, in accordance with national guidelines at the time of this trial, and noted in the hospital records. Children were registered and monitored through the CCLG Data Centre and followed until censor point or death.

### 2.2. Procedures

After maximal surgical resection, the chemotherapy schedule comprised blocks of alternating myelosuppressive and non-myelosuppressive drugs repeated at 14-d intervals to produce a high-intensity regimen with modest individual drug-dose intensity (Table 1). Drugs chosen had different mechanisms of cytotoxic action in an attempt to prevent the early emergence of drug resistance. Each course lasted for 56 d and a total of seven cycles were given. Children weighing 10 kg or more were dosed by surface area, those weighing less than 10 kg were dosed by weight as shown. Course 1; carboplatin (550 mg/m$^2$ or 20 mg/kg) over 4 h and vincristine (1.5 mg/m$^2$ or 0.05 mg/kg) intravenous bolus; course 2; methotrexate (8000 mg/m$^2$ or 250 mg/kg) and vincristine (1.5 mg/m$^2$ or 0.05 mg/kg); course 3; cyclophosphamide (1500 mg/m$^2$ or 50 mg/kg) over 4 h with prehydration and mesna; course 4; cisplatin (40 mg/m$^2$ for 48 h or 1.3 mg/kg). Further details of administration are given in Table 1. 10% of the total dose of methotrexate was given over the first hour then the remaining 90% was given intravenously over 23 h. Hydration with 0.18% NaCl + 2.5% dextrose + $NaHCO_3$ 50 mmol/L + KCl 20 mmol/L was given before, during and for at least 48 h after the methotrexate infusion was completed. Methotrexate serum concentration was measured at 24 h, 48 h and 72 h post infusion. Folinic acid rescue was a fixed dose of 15 mg starting 36 h after the beginning of the methotrexate infusion 3-hourly for five doses, then 6-hourly until serum methotrexate concentration was under 0.1 μmol/L ($<1 \times 10^{-7}$ M). Mesna was given alongside the cyclophosphamide (1800 mg/m$^2$ or 60 mg/kg) and was given intravenously commencing with prehydra-




§ Slides not submitted for central pathology review **2 post elective RTX ***Excluding 7 inoperable brainstem, 3 of whom had a biopsy; # Did not receive Radiotherapy

**Fig. 1 – Patient flow through the study. [§]Slides not submitted for central pathology review; [**]2 post elective RTX; [***]excluding 7 inoperable brainstem, 3 of whom had a biopsy; [#]did not receive radiotherapy.**

**Table 1 – Chemotherapy schedule.**

| 4 Courses to 1 cycle<br>7 Cycles in total | Children up to 10 kg (dose by weight) | Children > 10 kg (dose by surface area) |
|---|---|---|
| *Course 1; day 0* | | |
| Vincristine (iv bolus) | 0.05 mg/kg | 1.5 mg/m$^2$ |
| Carboplatin (iv over 4 h) | 20 mg/kg | 550 mg/m$^2$ |
| *Course 2; day 14* | | |
| Vincristine (iv bolus) | 0.05 mg/kg | 1.5 mg/m$^2$ |
| Methotrexate | 250 mg/kg | 8000 mg/m$^2$ |
| Folinic acid | 15 mg fixed dose | 15 mg fixed dose |
| *Course 3; day 28* | | |
| Vincristine (iv bolus) | 0.05 mg/kg | 1.5 mg/m$^2$ |
| Cyclophosphamide | 50 mg/kg | 1500 mg/m$^2$ |
| Mesna | 60 mg/kg | 1800 mg/m$^2$ |
| *Course 4; day 42* | | |
| Cisplatinum: (continuous infusion for 48 h) | 1.3 mg/kg × 2 d | 40 mg/m$^2$ × 2 d |

tion, continuing through 4-h cyclophosphamide infusion and ending 12 h after the completion of cyclophosphamide infusion. For cisplatin administration, prehydration included 0.45% saline + 2.5% dextrose, 200 mL/m$^2$ for 3 h. Hydration during and for 6 h post cisplatin was 0.45% saline + 2.5% dextrose + KCl 20 mmol/L + mannitol 12 g/L. Total intravenous infusion rate was equal to 125 mL/m$^2$/h for 48 h. Chemotherapy was to start within 4 weeks of surgery, and continued for 1 year unless there was unacceptable toxicity (determined by the treating physician), or until disease progression. Haematological toxicity alone was not an indication to delay treatment.

Radiotherapy was withheld unless there was progressive disease, when it was given with curative intent and was delivered using megavoltage photons on linear accelerators with custom made perspex shells. For tumours with a propensity to spread throughout the CSF (embryonal tumours and choroid plexus carcinoma) whole CNS radiotherapy was given with a boost to the primary tumour. The dose to the whole neuroaxis was 35 Gy in 21 daily fractions treating 5 d a week (1.67 Gy per fraction) for children of 3 years or older. For children aged less than 3 years, the craniospinal dose was reduced to 25 Gy in 20 daily fractions (1.25 Gy per fraction). The phase 2 volume was determined by the macroscopic tumour present at the time of radiotherapy with a 2 cm margin to account for microscopic disease and day to day set up variations. The dose prescribed to this volume was 20 Gy in 12 daily fractions of 1.67 Gy treating 5 d a week for all ages and sites. Astrocytomas were treated with local radiotherapy to the radiologically defined macroscopic tumour with a margin of 2 cm. For small field, sizes of less than 7 by 7 cm, beam-directed radiotherapy was recommended but larger tumours were treated with parallel-opposed fields. The dose prescribed was dependent on the field size, such that the dose for small volumes was 50 Gy in 25 daily fractions of 2 Gy per fraction treating 5 d per week and that for greater volumes 45 Gy in 27 daily fractions.

Following an interim analysis in January 1996 elective involved field radiotherapy was advocated for children with posterior fossa medulloblastoma.

### 2.3. Assessment

Patients were staged by full neuroaxis imaging; postoperative scans (within 48 h) were recommended, this was achieved in most but not all cases. All patients underwent primary surgery with the aim of achieving maximal surgical resection. A complete resection (R0) was recorded when there was no visible tumour documented by the surgeon at the end of operation, a subtotal resection when visible tumour remained (R1), and a biopsy when only sufficient tumour for diagnosis was removed (R3). The operative notes and postoperative scans were reviewed centrally (JAGP). Central radiological review of the extent of the surgical resection on postoperative scans was undertaken (TC, WKC and RG). Routine scans were requested on days 112, 224 and the end of the chemotherapy schedule. Cerebrospinal fluid [CSF] sampling prior to treatment was recommended, but central review of CSF cytology was not undertaken.

Central histopathological assessment of all tumours was undertaken (DWE and JWI) using standard tinctorial stains, and immunohistochemistry where necessary. Tumours were classified according to World Health Organisation 2007 (WHO) criteria.[11] Data analysis was on the basis of local and central review consensus diagnosis.

Toxicity was assessed by the treating physician and was coded in the CCLG data centre. The UKCCSG shortened listing of National Cancer Institute common toxicity criteria version 2.0 was used.

### 2.4. Statistical methods

Survival-to-progression (STP) was defined as the time from the date of surgery (date of diagnosis if surgery inappropriate) to the date of progression. Those who remain alive or die without progression and those who receive elective radiotherapy are censored at the corresponding date of the last follow-up, death or when radiotherapy began.

The cumulative time of need-for-radiotherapy for progression was calculated from the date of surgery to one of the following as appropriate: (i) date of the start of radiotherapy for progression, (ii) date of progressive disease if not followed by radiotherapy or (iii) date of death (taken as an indication of progression) if the patient died without receiving RT. Patients who were alive without progressive disease and not having received radiotherapy are censored at the date last seen. Patients receiving elective RTX prior to progression are censored at the date of the start of radiotherapy.

Event-free survival (EFS) was defined as the time from date of surgery to the date of the first event. An event was defined as recurrence or death. In those cases in which death followed recurrence the 'event' was the recurrence. Patients alive without recurrence were censored at the date last seen. Overall survival (OS) was calculated as the time from the date of surgery to death. Patients still alive were censored at the date last seen.

Survival probabilities were calculated using the Kaplan–Meier method. The hazard ratio (HR) and 95% confidence interval (CI) for comparing groups of patients was estimated using the Cox proportional hazards model. The potential influences of age, gender and tumour site on the HR were also investigated with the Cox model.[12]

Protocol chemotherapy received (PCR) was calculated for each patient as the proportion of the cumulative dose of the regimen actually received relative to the dose defined in the protocol (see Table 1). This would equal unity if the total chemotherapy dose received corresponded exactly to that specified in the protocol. The distribution and mean value of these ratios are then obtained for all patients and each tumour sub-type (Fig. 2). This calculation ignores the time period over which the chemotherapy is administered as compared to that defined in the protocol. The dose intensity (DI) adjusts the individual patient PCR by the ratio of the actual time the regimen took to be given divided by the corresponding protocol defined time. This would equal unity if the chemotherapy total dose received and the time taken corresponded exactly to that specified in the protocol. The distribution and mean value of these time-adjusted ratios are then obtained (Fig. 2).

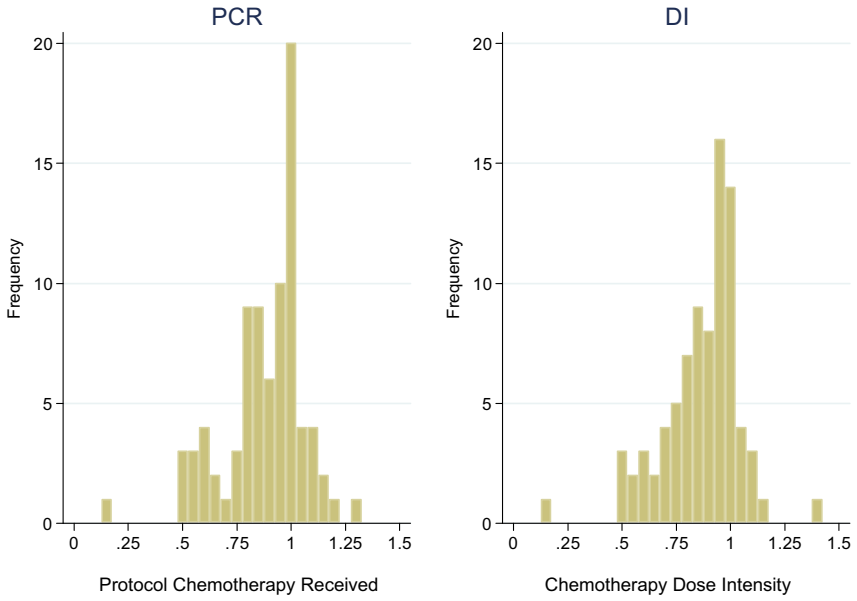



**Fig. 2 – Distributions of protocol chemotherapy received (PCR) and the corresponding dose intensity (DI).**

## 3. Results

### 3.1. *Study population*

Between December 1992 and July 2003, 97 patients were recruited from 6 diagnostic categories: astrocytoma, medulloblastoma, choroid plexus carcinoma (CPC), central nervous system primitive neuroectodermal tumour (CNS PNET), atypical teratoid tumour/rhabdoid tumour (AT/RT) and other (including 2 initially thought to be ependymoma). Follow-up of survivors is ongoing.

Recruitment of children with primitive neuroectodermal tumours was suspended in September 1996 following interim analysis that showed a 1-year EFS of 0% at that time for CNS PNET. The study was closed to choroid plexus tumours and high-grade gliomas in August 2001. One additional case, a CPC was recruited in July 2003 and has been included as full follow-up details are available. Patient flow through the study is shown in Fig. 1. Following central pathological review, 13 of 89 patients (15%) had their diagnosis changed as detailed in Table 2. There were also 7 who had low-grade astrocytoma and 1 had germ cell tumour for whom the protocol was not intended and these are not discussed further as they are ineligible. The final diagnoses of eligible patients were medulloblastoma ($n = 31$), astrocytoma (26) and with fewer CPC (15), CNS PNET (11) and AT/RT (6). The median follow-up for all 89 eligible patients is 1.1 years (range 0.07–13.2), 21/89 (24%) of whom remain alive with median follow-up of 8.04 (1.21–13.2) years. Overall 45/89 (51%) had pre-chemotherapy CSF sampling, 13 as part of myelography examination; this varied by diagnosis with only 5/26 (19%) of patients with glioma versus 21/42 (50%) of those with medulloblastomas or PNETs. Overall 4 cases had malignant cells identified in the CSF; 2 Medulloblastoma, 1 CNS PNET and 1 CPC. Seventy six of 89 patients had whole axis neuro-imaging, again spinal imaging was not performed on those thought less likely to have spinal metastases.

**Table 2 – Local versus central pathology panel review.**

| Case no. | Local diagnosis | Review diagnosis |
|---|---|---|
| 1 | Astrocytoma | CNS PNET |
| 2 | Astrocytoma | CNS PNET |
| 3 | Choroid plexus carcinoma | ATRT |
| 4 | Choroid plexus carcinoma | Medulloblastoma |
| 5 | Medulloblastoma | Germ cell tumour |
| 6 | Medulloblastoma | High-grade glioma |
| 7 | Medulloblastoma | ATRT |
| 8 | Other | ATRT |
| 9 | Other | Medulloblastoma |
| 10 | Other | HGG |
| 11 | Other | HGG |
| 12 | Other | HGG |
| 13 | Other | HGG |

## 4. Implementation of treatment strategy

### 4.1. *Surgery*

Excluding brain stem gliomas ($n = 7$), for whom a primary surgical strategy was not advocated, 26% (21/82) eligible cases underwent surgery and achieved a complete resection. A partial resection was obtained in 56% (46/82) and 17% (14/82) had a biopsy only.

### 4.2. *Chemotherapy received and associated toxicity*

Following surgery the median time to starting chemotherapy was 16 d (range 0–199). Chemotherapy for 330 d or more was completed in 25/89 (28%) patients of whom all but 3 (3%) completed 7 cycles. The median protocol chemotherapy received (PCR) was 0.93 relatively close to the ideal of 1 but ranged

**Table 3 – Protocol chemotherapy received and dose intensity achieved by diagnostic group.**

| | | Medulloblastoma | Astrocytoma | CPC | sPNET | AT/RT | Total |
|---|---|---|---|---|---|---|---|
| Received chemotherapy | | 29 | 24 | 13 | 11 | 6 | 83 |
| PCR | Minimum | 0.52 | 0.53 | 0.50 | 0.15 | 0.83 | 0.15 |
| | Median | 0.90 | 0.96 | 0.93 | 0.97 | 0.98 | 0.93 |
| | Maximum | 1.28 | 1.22 | 1.17 | 1.12 | 1.12 | 1.28 |
| | ⩾1 | 6 | 7 | 3 | 4 | 2 | 22/89 (25%) |
| DI | Minimum | 0.52 | 0.53 | 0.50 | 0.15 | 0.83 | 0.15 |
| | Median | 0.84 | 0.91 | 0.89 | 0.96 | 0.97 | 0.90 |
| | Maximum | 1.41 | 1.11 | 1.05 | 1.12 | 1.14 | 1.41 |
| | ⩾1 | 14 | 9 | 4 | – | 1 | 28/89 (31%) |

from 0.15 to 1.28 of that intended (Fig. 2, Table 3). The corresponding median dose intensity (DI) was 0.90 (0.15–1.41). Although there was a considerable variation across the histological groups, 22/89 (25%) received only the first cycle of chemotherapy while a similar proportion 21/89 (24%) received all the cycles.

The majority, 62/89 (70%), experienced grade 4 haematological toxicity, 2 patients experienced grade 3 and 1 patient experienced grade 4 renal toxicity and 1 patient experienced grade 4 ototoxicity. There were no deaths clearly attributable to chemotherapy toxicity.

Amongst those who received 6 or more cycles there was a suggestion of improved OS in those with the higher DI but numbers are very small and the trend contradictory in those having fewer cycles of treatment.

### 4.3. *Radiotherapy*

In total, 72/89 (81%) of the patients have progressed including 2 (at 0.73 and 1.00 years post surgery) of 7 who had received prior elective radiotherapy. The STPs at 1, 2 and 3 years are 59.9%, 78.6% and 81.7%, respectively (Fig. 3) although these vary considerably depending on the patient diagnostic category. Subsequently 29 were irradiated for their progression with need-for-radiotherapy rates of 28.3%, 51.3% and 54.6% at 1, 2 and 3 years. The median time to radiotherapy for progression was 8.44 months (range 1.61–50.10) and the median age at radiotherapy for progression was 2.99 years (range 1.6–5.9 years) – 15 aged less than 3 years. Of those metastatic at diagnosis 14/25 (56%), including 3 elective, were irradiated. In all 53/89 (60%) children were not irradiated of whom 41 (77%) progressed.

## 5. Outcome by diagnostic category

### 5.1. *Medulloblastoma*

There were 31 patients diagnosed with medulloblastoma and histopathology review classified the majority, 17 (55%), as desmoplastic/nodular (D/N).[13] Of these 10 were 'typical' D/N tumours and 7 were classified as medulloblastoma with extensive nodularity (MBEN). Although these tumours have been associated with a better prognosis,[14] due to the small number of MBEN cases in this series they were not analysed separately. The remainder were either classic tumours, 6 (19%), or large cell/anaplastic variants (LC/A), 5 (16.1%) (Table

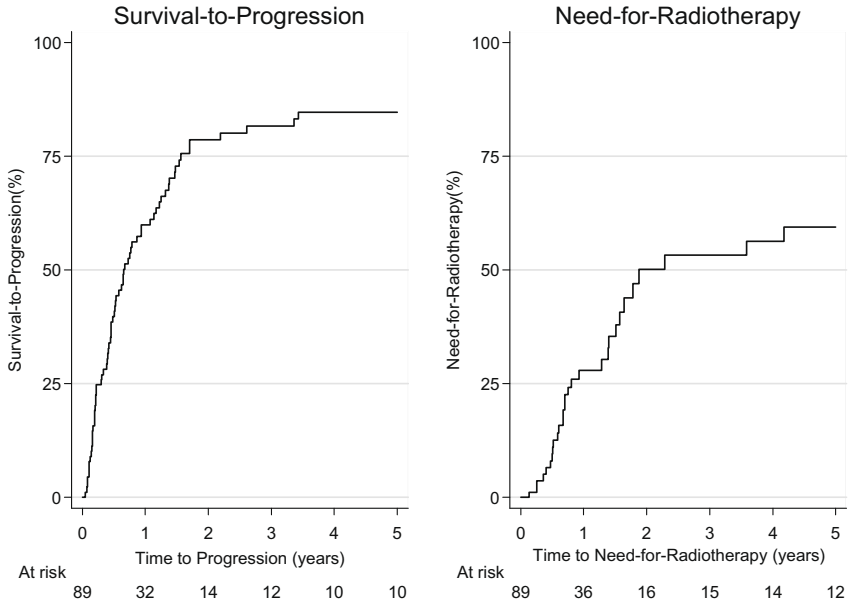



**Fig. 3 – Survival-to-progression and need-for-radiotherapy.**

4). Of these 15/31 (48%) had overt metastatic disease (1 M2, 14 M3) at diagnosis, 11 (35%) others had a postoperative local residuum giving 26 (84%) with radiological evidence of residual disease. There was no apparent association between histopathological variant and metastatic disease. At a median follow-up of live patients of 9.89 years (range 5.22–13.22 years), 23 (74%) patients have progressed, 15 (65%) with leptomeningeal disease, and 21 (68%) have died.

A total of 14 patients completed chemotherapy 2 of whom were electively irradiated without progression. There were 2 additional patients who stopped chemotherapy early and were subsequently irradiated without evidence of disease progression, 1 of whom had reached 3 years of age while 12 patients were irradiated following disease progression. The median time to radiotherapy for progression was 12.6 months (range 3.1–43.0), with cumulative need-for-radiotherapy rates at 3 and 5 years of 62.6% (CI: 37.9–86.8) and 71.9% (CI: 46.3–92.6).

The median overall survival was 1.74 years (range 0.22–13.22) for all patients. Three children, who received chemotherapy as their sole adjuvant treatment and are alive without disease progression at 9.82, 9.96 and 9.97 years (R0M3, R1M0 and R1M0, respectively), had D/N disease. Of the 23 patients who progressed and were retreated, 12 received cranio-spinal radiotherapy (alone or in combination with further resection and/or chemotherapy), 11 others had either chemotherapy alone or palliative care.

To date 10 patients remain alive including 5 who presented with metastatic disease. Those with D/N had the best 5-year OS of 52.9% (Table 3). This reduced to 33.3% and 0.0% for classic and LC/A, respectively, with all 5 children of the latter group dying within 1 year of diagnosis (Fig. 4). Gender, age at diagnosis, presence or absence of metastatic disease or degree of resection had no demonstrable influence on survival. Overall, the salvage rate following cranio-spinal radiotherapy at relapse was poor.

**Table 4 – Characteristics of patients with infratentorial medulloblastoma at diagnosis and details of subsequent treatment and outcome.**

| Histology | | D/N | Classical | LC/A | Undetermined |
|---|---|---|---|---|---|
| Site | Infratentorial | 17 | 6 | 5 | 3 |
| Gender | Male | 11 | 3 | 1 | 2 |
| Age (years) | <1 | 7 | 2 | 2 | – |
| | Median | 1.78 | 1.77 | 2.50 | 1.77 |
| | Range | 0.20–2.75 | 0.80–2.42 | 0.38–2.64 | 1.50–2.09 |
| Metastatic | Disease | 7 | 4 | 2 | 2 |
| Surgical resection | Total | 8 | 2 | 2 | 1 |
| | Partial | 8 | 4 | 3 | 1 |
| | Biopsy | 1 | – | – | 1 |
| Tumour stage[15] 4 | R0M0 | 3 | – | 1 | 1 |
| Residual tumour and/or metastatic | R1M1 | – | – | 1 | 1 |
| | R0M2 | 1 | – | – | – |
| | R0M3 | 4 | 2 | 1 | – |
| | R1M0 | 6 | 2 | 2 | – |
| | R1M3 | 3 | 2 | 1 | 2 |
| Surgery to chemotherapy (days) | >50 | 1 | – | – | – |
| | Median | 18.0 | 15.0 | 19.0 | 8.0 |
| | Range | 11–78 | 8–20 | 13–40 | 3–8 |
| Chemotherapy | Completed | 12 | 1 | – | 1 |
| RTX | Elective | 3 | 2 | – | – |
| No RTX | No recurrence | 3 | – | – | – |
| No RTX | Recurrence | 5 | 1 | 4 | 1 |
| RTX | Recurrence | 6 | 3 | 1 | 2 |
| Event-free survival (%) | 1-year | 88.2 | 33.3 | 0.0 | 33.3 |
| | 95% CI | 60.6–96.9 | 4.6–67.6 | – | 0.9–77.4 |
| | 3-year | 41.2 | 33.3 | – | 0.0 |
| | 95% CI | 18.6–62.6 | 4.6–67.6 | – | – |
| | 5-year | 35.3 | 33.3 | – | – |
| | 95% CI | 14.5–57.0 | 4.6–67.6 | – | – |
| Alive | | 8 | 2 | – | – |
| Overall survival (%) | 1-year | 94.1 | 83.3 | 0.0 | 66.7 |
| | 95% CI | 65.0–99.2 | 27.3–97.5 | – | 5.4–94.5 |
| | 3-year | 64.7 | 33.3 | – | 33.3 |
| | 95% CI | 37.7–82.3 | 4.6–67.6 | – | 0.9–77.4 |
| | 5-year | 52.9 | 33.3 | – | – |
| | 95% CI | 27.6–73.0 | 4.6–67.6 | – | – |

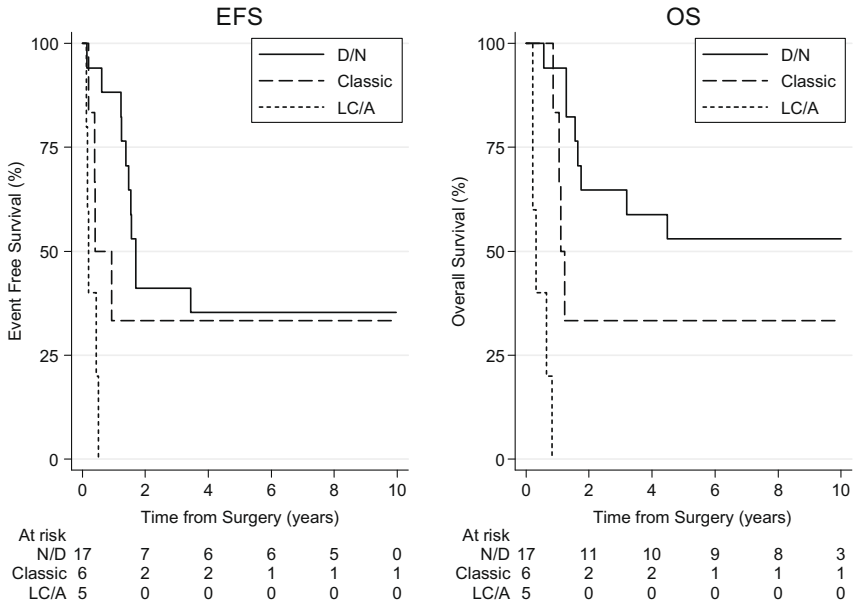



**Fig. 4 – EFS and OS in histological subgroups of children with medulloblastoma.**

### 5.2. *Astrocytoma*

The clinical features and surgical outcomes for the 26 children with astrocytoma are summarised in Table 5. Of these only 3 patients received a total resection and 22 (85%) have progressed. The cumulative radiotherapy rate for progression was 49.6% (95% CI: 24.7–78.0) at 5 years. The 3- and 5-year EFS are 17.6% (CI: 5.8–34.7) and 13.2% (CI: 3.4–29.6) with a median event-free survival of 0.53 years.

Following central pathology review, it was evident that astrocytomas of early childhood were a very heterogeneous group (Table 6).

Children with DIPGs had the worst outcome (Fig. 5) with all 7 patients progressing on chemotherapy. The median time to progression was short, 0.21 years (range 0.10–0.53 years). Only 2 patients were irradiated for progression. Both received 55 Gy to the tumour and were the longest living survivors at 0.87 and 1.43 years. The median OS was 0.30 years (range 0.25–1.43).

Seven of the 18 patients with HGG are long-term survivors beyond 4 years of whom 2 had grade IV glioblastoma; 2 anaplastic astrocytoma; 1 anaplastic oligodendroglioma; and 2 unclassified. Only one of these 6 patients underwent a total resection and one received radiotherapy. Two patients had recurrent disease and are alive following further surgery and chemotherapy at 5.5 and 6.1 years post recurrence.

### 5.3. *Choroid plexus carcinoma (CPC)*

Fifteen (5 posterior fossa, 10 supratentorial) patients with CPC were treated on this protocol (Table 7). Eleven patients progressed on chemotherapy and died; all with progression at the primary site and one with additional leptomeningeal disease. Only 2 of 15 cases (13%) underwent complete surgical resection. Time to progression was short, median 0.46 years (range 0.07–1.13 years). Four patients responded to chemotherapy. These comprised 3 patients who underwent subtotal resections, one of whom also had leptomeningeal deposits, and one patient with a large residual tumour mass following biopsy. Two of these patients had further surgery. All 4 are alive without irradiation at 5.00; 6.28; 9.21 and 10.21 years (Fig. 6). The 3- and 5-year OS is 26.7% (CI: 8.3–49.6) being best for those with a supratentorial site. One child was moribund at diagnosis but was treated by parental request dying 1 d (26 d post biopsy) after chemotherapy was initiated.

### 5.4. *Central nervous system primitive neuroectodermal tumour (CNS PNET)*

Eleven patients had CNS PNET, 2 had complete resection, 5 subtotal resections and 4 were biopsied (Table 6). Ten progressed on chemotherapy; the EFS was 45.5% at 6 months, all but 1 progressed/relapsed within 1 year (range 41 d–1 year) with 1-year OS of 9.1% (CI: 0.5–33.3) (Fig. 6). Seven children relapsed locally and 3 had local and metastatic relapse; 6 received radiotherapy, 2 electively and 4 at relapse, of which 3 had cranio-spinal irradiation; all subsequently progressed. One child rapidly deteriorated following chemotherapy with cisplatin and appears to have coned; potentially due to high volume fluid infusion in a child with raised intracranial pressure.

### 5.5. *Atypical teratoid/rhabdoid tumours (AT/RT)*

Six patients had AT/RT, of these 1 had multifocal disease with tumour in the posterior fossa supratentorium and spine and 1 had M3 disease. All underwent surgery, 1 had a complete resection, 4 a subtotal resection and 1 a biopsy (Table 6). All progressed on chemotherapy before 3 years with the corresponding OS at the time of 16.7% (CI: 0.8–51.7%) and had died within 4 years of diagnosis (Fig. 6). Six children relapsed locally,

**Table 5 – Characteristics of patients with astrocytoma at diagnosis and details of subsequent treatment and outcome.**

| | | High grade (HGG) | Brain stem (DIPG) |
|---|---|---|---|
| Number | | 19 | 7 |
| Gender | Male | 14 | 4 |
| Age (years) | <1 | 6 | 1 |
| | Median | 1.80 | 2.52 |
| | Range | 0.33–3.09 | 0.68–3.01 |
| Metastatic disease | | 3 | – |
| Site | Posterior fossa | 2 | – |
| | Supratentorial | 17 | – |
| | Brain stem | – | 7 |
| Surgical resection | Total | 3 | – |
| | Partial | 11 | – |
| | Biopsy | 5 | 3 |
| | Inoperable | – | 4 |
| CSF | M1 | – | – |
| Surgery to chemotherapy (days) | >50 | 1 | – |
| | Median | 15 | 7 |
| | Range | 4–199 | 0–24 |
| Chemotherapy | Completed | 6 | – |
| No RTX | No recurrence | 4 | – |
| No RTX | Recurrence | 10 | 5 |
| RTX | Recurrence | 5 | 2 |
| Event-free survival (%) | 1-year | 52.6 | 0.0 |
| | 95% CI | 28.7–71.9 | – |
| | 3-year | 24.1 | – |
| | 95% CI | 7.8–45.1 | – |
| | 5-year | 18.1 | – |
| | 95% CI | 4.6–38.6 | – |
| Alive | | 7 | – |
| Overall survival (%) | 1-year | 57.9 | 14.3 |
| | 95% CI | 33.2–76.3 | 0.7–46.5 |
| | 3-year | 40.5 | 0.0 |
| | 95% CI | 18.7–61.5 | – |
| | 5-year | 34.7 | – |
| | 95% CI | 14.6–56.0 | – |

**Table 6 – Identified sub-types of astrocytoma following pathology review.**

| WHO | High-grade glioma HGG (18) | Diffuse pontine glioma DIPG (7) |
|---|---|---|
| II | – | Diffuse astrocytoma (1) |
| III | Anaplastic Astrocytoma (7)<br>Astroblastoma (1)<br>Anaplastic oligodendroglioma (2) | – |
| IV | Glioblastoma (5) | Glioblastoma (1) |
| Unclassified | (1) | (1) |
| Inoperable | – | (4) |
| Unknown | (2) | – |

1 had a local and metastatic relapse and for one child site of relapse was unknown. Two received radiotherapy at relapse, of whom 1 had cranio-spinal irradiation, without benefit.

### 5.6. *Late effects*

The long-term follow-up data on the survivors on this CNS 9204 study have been extracted from the yearly study follow-up forms. Overall there are 21 children still alive, of whom 8 were irradiated. There are a wide range of disabilities from no reported problems to five separate categories of morbidity, including special educational needs, developmental delay, cerebellar dysfunction, epilepsy; visual filed defects, hearing loss, endocrinopathy and behavioural problems. Moreover the problems reported range from mild to severe only 1 child is reported to have no problems, 2 are reported to have mild cerebellar dysfunction alone and 2 others have restricted visual fields as only reported late effects. Five children required 'special needs' education, 7 have significant endocrinopathy, 5 children are reported to have behavioural problems with 2 having autitic spectrum disorder. Overall, children who were irradiated accumulated more categories and more severe long-term disability.

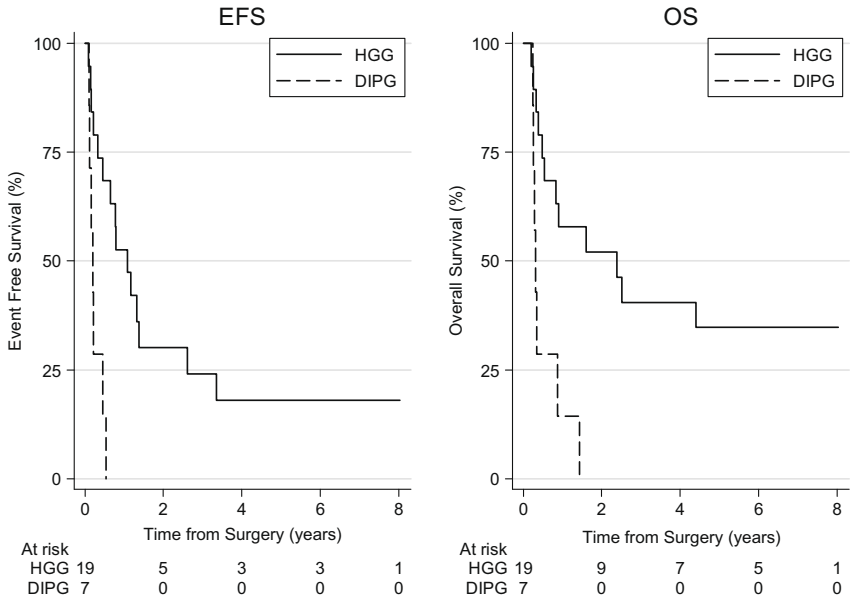



**Fig. 5 – EFS and OS for children with high-grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG).**

**Table 7 – Characteristics of patients with CPC, CNS PNET and AT/RT at diagnosis and details of subsequent treatment and outcome.**

| | | CPC | CNS PNET | AT/RT |
|---|---|---|---|---|
| Number | | 15 | 11 | 6 |
| Gender | Male | 14 | 6 | 3 |
| Age (years) | <1 | 9 | 3 | 3 |
| | Median | 0.87 | 1.21 | 0.92 |
| | Range | 0.35–2.87 | 0.23–2.55 | 0.10–2.61 |
| Metastatic disease | | 4 | 1 | 2 |
| Site | Posterior fossa | 5 | – | 2 |
| | Supratentorial | 10 | 8 | 3 |
| | Pineal | – | 3 | – |
| | Cervico-dorsal | – | – | 1 |
| Surgical resection | Total | 2 (13%) | 2 (18%) | 1 (17%) |
| | Partial | 10 | 5 | 4 |
| | Biopsy | 3 | 4 | 1 |
| CSF | M1 disease | 1 | 1 | – |
| Surgery to chemotherapy (days) | >50 | – | – | – |
| | Median | 21.0 | 22.0 | 9.5 |
| | Range | 7–43 | 4–39 | 1–49 |
| Chemotherapy | Completed | 1 (7%) | – (0%) | 1 (17%) |
| RTX | Elective | – | 2 | – |
| No RTX | No recurrence | 4 | 1 | – |
| No RTX | Recurrence | 7 | 4 | 4 |
| RTX | Recurrence | 4 | 4 | 2 |
| Event-free survival (%) | 1-year | 28.9 | 0.0 | 16.7 |
| | 95% CI | 9.0–2.8 | – | 0.7–51.7 |
| | 3-year | 21.7 | – | – |
| | 95% CI | 5.3–45.1 | – | – |
| | 5-year | 21.7 | – | – |
| | 95% CI | 5.3–45.1 | – | – |
| Alive | | 4 | – | – |
| Overall survival (%) | 1-year | 50.3 | 9.1 | 50.0 |
| | 95% CI | 23.1–72.4 | 0.5–33.3 | 11.1–80.4 |
| | 3-year | 21.5 | – | 16.7 |
| | 95% CI | 5.2–45.0 | – | 0.8–51.7 |
| | 5-year | 21.5 | – | – |
| | 95% CI | 5.2–45.0 | – | – |

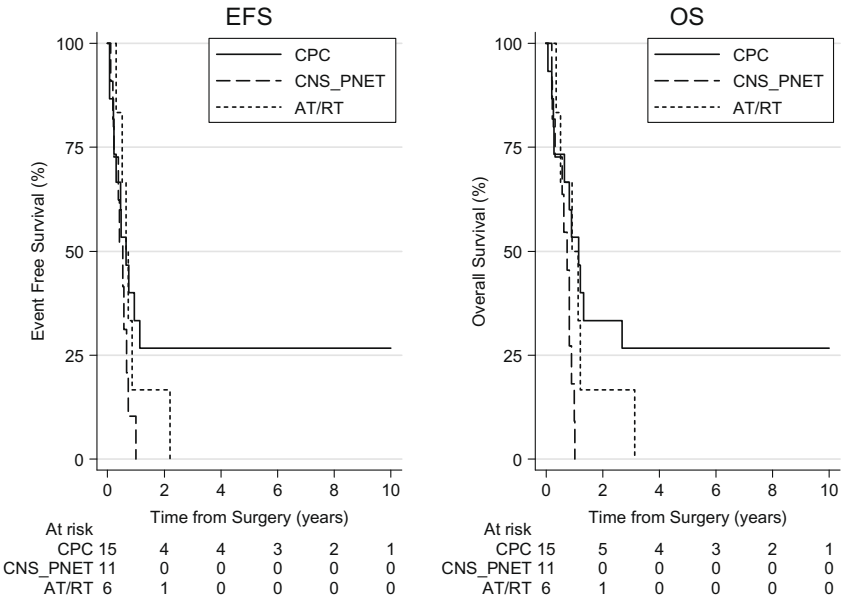



**Fig. 6 – EFS and OS in children with CPC, CNS PNET and AT/RT.**

## 6. Discussion

The UKCCSG 9204 study reported here with its long-term follow-up was one of the 'first generation baby brain studies' in which chemotherapy, relatively high intensity, was explored principally in an attempt to either delay or avoid the use of radiotherapy in very young children with CNS tumours. In these studies, the protocol was applied to a variety of tumour types with, as in the study reported here, different outcomes dependent on tumour types and in some cases histological sub-type. Although, it is now clear that the treatment of CNS tumours in this age group requires tumour-specific protocols, this and the other baby brain trials have provided valuable information with respect to their natural history, treatment responsiveness and outcome.

These early studies differed in the nature of the chemotherapy used and in the recommendations for radiotherapy. The UKCCSG 9204 study was unique in that it employed alternating courses of myelosuppressive and relatively non-myelosuppressive chemotherapy to enhance treatment intensity with chemotherapy given every two weeks. High-dose methotrexate (8 g/m$^2$) was delivered systemically every course, but was not given by intrathecal or by the intraventricular route. Radiotherapy was only given for progression, as opposed to the POG study in which radiotherapy was routinely given at the end of chemotherapy.[7]

The median time to radiotherapy was 22 months with a median age of 3 years at irradiation, thereby achieving one of the aims of this protocol. Overall, 45% of our cohort were not irradiated for the progression of disease, however, this might under estimate the true 'radiotherapy free survival' as some patients may not have been offered radiotherapy for ethical reasons after physician discussions with parents and some might have deteriorated before radiotherapy could be delivered. Additionally a small number of children, particularly those with medulloblastoma, were electively irradiated at the end of chemotherapy. In contrast to our study of ependymoma cases, the small number of patients in each of the heterogeneous tumour types prevented a meaningful assessment using competing risks.[10,16] We investigated whether there was a relationship between received intended dose intensity and survival. However, unlike the ependymoma cohort, for whom 89 patients were evaluable,[10] the limited number of cases in each of the tumour types in this study made it difficult to draw firm conclusions on the role of dose intensity on outcome.

This study was started at a time when there was still considerable ethical debate about treatment strategies for brain tumours in very young children. Excluding diffuse pontine gliomas the overall complete resection rate was only 26% and the resection rates by tumour type were lower than many other reported series. This might either reflect extreme caution for ethical reasons of avoiding risk of injury by neurosurgical colleagues or a belief in the power of chemotherapy to eradicate residual disease post surgery.

One of the central questions in improving outcome for young children with brain tumours is the extent to which outcome is predetermined by biological factors versus treatment decisions. This is most evident in the medulloblastoma cohort, in which the desmoplastic/nodular (D/N) variant was associated with a significantly better outcome, confirming the findings of Rutkowski et al.[17] D/N architecture is seemingly a more powerful prognostic factor than traditional adverse features of incomplete resection and metastatic disease in our high-risk population. Our 5-year event-free survival at 35% is similar to the POG 9921 but considerably lower than the 58% overall progression-free survival reported by the German group. Similarly, the 5-year overall event-free survival of children with D/N medulloblastoma in our cohort was 53%, markedly better than that for patients with classic histological medulloblastoma [5 yr EFS 33% (95% CI)], but inferior to the HIT-SKK'92 trial, in which children without resid-

ual tumour have an overall survival of 93% whilst 56% of those with residual tumour are long-term survivors.[17] However, only 5 patients (16%) of our population had a complete resection and no evidence of metastatic disease [T0M0] compared to 40% in the SFOP study and CCG-991 and 72% in the SKK study.[15,17] There is considerable interest in the debate over the role of methotrexate in the management of childhood brain tumours. The best results to date in medulloblastoma have been achieved with the concomitant use of intraventricular and high-dose intravenous methotrexate.[17] The IQ data suggest that the neuro-cognitive sequel is acceptable, but considerable concern has been raised by the degree of leukoencephalopathy in the HIT-SKK study.[17] The UK protocol used high-dose methotrexate and as previously reported, few of our long-term survivors had evidence on MR scans or leukoencephalopathy.[10]

Molecular analyses have identified that D/N medulloblastomas have distinct gene expression patterns, a number of which harbour inactivating mutations in the Sonic Hedgehog pathway, which in turn may offer opportunities for novel therapy.[18–20] The future will involve determining the optimal chemotherapy strategy, appraisal of the role of biological therapies and a re-evaluation of the role of limited radiotherapy both in field and in dose. Very young children with minimal residual disease post operatively can potentially be cured by conventional +/– intraventricular chemotherapy if they have desmoplastic medulloblastomas. A meta-analysis of infant medulloblastoma may help better define these factors and inform the international effort in the development of new trials.

This study adds to the body of evidence suggesting that young patients with malignant astrocytoma have a better outcome than older children and adults, with a 5-year OS ranging from 36% to 66%.[7,21,22] Important variables in published studies include differences in histopathological classification, degree of surgical resection and timing of radiotherapy. It is clear that expert pathological review is essential for the classification of infant astrocytomas, in this study 6 patients had their diagnosis changed following central review. Similarly, in the POG study 9 of 18 could only be classified as 'malignant astrocytoma' and, in CCG-945, 18% of HGG were reclassified.[7,21,23] The St Jude series 25% were re-graded.[24] Similar findings were reported in older children on CCG-945.[25] The report from the SFOP study found 33% of patients had grades II and III oligodendrogliomas far higher than in other series.[22] In CCG-945 the institutional diagnosis of grade III oligodendrogliomas or mixed astrocytomas was confirmed in only 50% of cases.[26] Histology was not representative of outcome in our series, as in others, although this may simply reflect small sample size.

The role and timing of radiotherapy for astrocytomas remains controversial. All children on the POG study were routinely irradiated,[7] whilst the single institution study from St Jude concludes that most children require irradiation despite the high morbidity and poor neuro-cognitive outcomes of their cohort.[24] In our study, the cumulative radiotherapy rate was 29% at 5 years suggesting that a subset of cases is potentially curable without radiotherapy. Recently reported results from the French baby brain protocol report 59% overall survival at 5 years, with 10 of the 12 long-term survivors being cured without radiotherapy.[22] Overall, a proportion of supratentorial high-grade astrocytomas have a durable response, without radiotherapy, to regimens containing alkylating and platinum agents with or without methotrexate. Identifying these patients up front is our next challenge, but will require international collaboration.

No child with a brain stem astrocytoma survived irrespective of histological grade reflecting the failure of any chemotherapeutic or radiation regime to impact on this disease.[27,28]

Choroid plexus carcinoma (70%) occurs in children under 2 years of age.[29] Radical surgical resection is difficult due to the highly invasive, vascular nature of this malignancy that also demonstrates a propensity to metastasis. Indeed, complete resection was only achieved in only 2 of 15 patients (14%) in our cohort, compared to 30–50% in other large series.[30,31] All survivors obtained radiological remission by chemotherapy alone or in combination with a second-look operation, confirming the importance of surgery and the role of chemotherapy in increasing operability and opportunity for radiological remission.[32,33] Tumour location was an important factor with supratentorial tumours having a significantly better outcome; this was not simply related to operability as complete resection was achieved in only 2 cases. This trial recruited a relatively large number of patients with choroid plexus carcinoma and demonstrates that a subset of these tumours can be cured without radiotherapy in agreement with other studies.[30,31,34]

This study included a small number of atypical teratoid/rhabdoid tumours, for whom the prognosis was very poor with no long-term survivors. The literature supports a tendency to a better outcome with complete resection, but this was only achieved in one case. The role of intrathecal/intraventricular chemotherapy in this disease remains unclear but deserves further study as does the role of high-dose chemotherapy.

Children with CNS PNETs progressed rapidly on this protocol with no long-term survivors. The majority of patients progressed locally emphasising on the importance of local control. The more recent CCG-9921 study demonstrated that although the event-free survival is poor some patients with CNS PNET may be salvaged (5 year EFS 17%, OS 31%), although the details of salvage therapy are not provided.[34]

This study contributes to the increasing body of knowledge regarding attempts to spare the brain during the treatment of brain tumours in young children. A consistent theme from this study over a prolonged recruitment period is the conservative approach to surgical resection adopted in these patients which, on comparison with previously published, yet contemporaneously conducted trials, differ considerably and would seem to account for the major difference in survival rates where this exists. This conclusion justifies the strategic centralisation of neurosurgical services for children in the UK as a result of Department of Health Strategy. Different histological types have different outcomes with this standardised chemotherapy approach confirming the correlation between biological diversity, as judged histologically, and sensitivity to chemotherapy agents. Comparisons of tumour sensitivity in these rare tumour types are valuable as experience is slow to accrue and planning future studies requires such data for optimised drug selection. We

cannot conclude from this study that the strategy was brain sparing because of the lack of neuro-cognitive testing of this cohort. This highlights on the need for having such assessments built into the late evaluation of survivors in the next generation of international studies but also the standard to be expected for clinical practice in this group of seriously ill young children. Future progress will depend on developing optimised surgical strategies, and designing chemotherapy/drug strategies for trial which are tailored to different biological categories and selecting, on first principles, the least radiation dose that can be considered effective for the areas of brain with highest risk of recurrence. The rarity of these tumours in this early stage in life means that international collaboration will be necessary.

## Conflict of interest statement

None declared.

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