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Outcome for patients with metastatic (M2–3) medulloblastoma treated with SIOP/UKCCSG PNET-3 chemotherapy

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Abstract

The aim of this study was to determine the outcome for patients with Chang stage M2–3 medulloblastoma (MB) treated with surgery and pre-radiotherapy (RT) chemotherapy (CT). Between 1992 and 2000, 68 patients aged 2.8–16.4 years (median 7.8 years) with M2–3 MB were treated with CT comprising vincristine, etoposide, carboplatin and cyclophosphamide. For 61 patients, CT was followed by craniospinal RT 35 Gy/21 fractions with a posterior fossa (PF) boost, 20 Gy/12 fractions. Twenty-four (35%) irradiated patients received a metastatic boost (mean dose to metastases 47.4 Gy, range 40.0–55.1 Gy). With 7.2-years of median follow-up, overall survival (OS) rates at 3 and 5 years were 50.0% (95% Confidence Interval (CI): 38.1–61.9%) and 43.9% (95% CI: 32.0–55.7%), respectively, event-free survival (EFS) rates at 3 and 5 years were 39.7% (95% CI: 28.1–51.3%) and 34.7% (95% CI: 23.2–46.2%), respectively. Univariate analysis did not demonstrate an impact of age, gender, M stage, extent of resection, RT duration or metastatic boost. For patients commencing RT within 110 days of surgery, EFS was significantly ($P = 0.04$) worse than for those who commenced RT later than this. Response to pre-RT CT was assessable from institutional reports for 44 (65%) patients, and 17 (39%) had a complete response (CR), 15 (34%) a partial response (PR), 4 (9%) stable disease (SD) and 8 (18%) progression. Although CT improved outcome for M0-1 patients in the primitive neuroectodermal tumour (PNET-3) randomised study, and resulted in a high response rate in this study, there has been no apparent improvement in outcome for M2–3 patients when compared with earlier multi-institutional series. Newer approaches such as more intensive CT and RT need to be explored.

Keywords: Medulloblastoma; Metastases; Chemotherapy; Radiotherapy; Outcome; Survival

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1. Introduction

Medulloblastoma (MB) is a primitive neuroectodermal tumour (PNET) arising in the cerebellum, and accounts for approximately 20% of paediatric brain tumours. They have a propensity for leptomeningeal spread and approximately 30–35% present with evidence of metastatic disease, either in the supratentorial meninges (Chang stage [1] M2) or spinal canal (Chang stage M3).

In current multi-institutional protocols, treatment is stratified according to the allocation of risk status. Standard-risk patients have no evidence of leptomeningeal metastases (Chang stage M0) and less than 1.5 cm^2 of residual tumour on a post-operative magnetic resonance (MR) scan. High-risk patients include those with significant post-surgical residue, with cells in lumbar cerebro-spinal fluid (CSF) (Chang stage M1) or with 'solid' metastases (Chang stages M2–3). Outcomes for standard-risk patients are good with progression or event-free survival (EFS) rates of least 70–80% [2,3]. However, the outcome for patients with M2–3 disease remains relatively poor [4–7].

The International Society of Pediatric Oncology/United Kingdom Children's Cancer Study Group (SIOP/UKCCSG) PNET-3 study recruited patients between 1992 and 2000. Patients with medulloblastoma and no evidence of metastases on cranial computerised tomography (CT) or MR and spinal MR or myelogram (M0-1) were randomised to treatment with RT alone or preceded by four cycles of CT comprising vincristine, etoposide and alternating carboplatin and cyclophosphamide. The results of this study have been reported in Ref. [3]. EFS was significantly better for patients treated by CT and RT (EFS 78.5% at 3 years and 74.2% at 5 years) compared with RT alone (EFS 64.8% at 3 years and 59.8% at 5 years). Overall survival (OS) was 83.0% at 3 years and 76.7% at 5 years for CT and RT compared with 76.1% at 3 years and 64.9% for RT alone, but this difference was not statistically significantly different.

Efforts to improve outcome for patients with high-risk disease have concentrated on the role of CT in addition to RT.

During the time that the PNET-3 study was recruiting, it was recommended that patients with M2–3 disease should be treated with CT followed by RT. The outcome for these patients has been analysed. Since patients with M2–3 disease were not included in the randomised study, comparison has to be made with other series of patients with M2–3 disease, although it has to be accepted that differences in selection criteria between different studies can influence comparative outcomes.

2. Patients and methods

2.1. Aims of the study

The main aim of this study was to report the outcome for patients with Chang stage M2–3 MB treated with PNET-3 pre-RT CT.

2.2. Pre-treatment investigations

It was mandatory that patients should have a spinal MR or myelogram prior to, or within 2 weeks after surgery, and a cranial CT or MR scan within 48–72 h after surgery. However, these recommendations were not always adhered to. Scans were not centrally reviewed. CSF sampling, although recommended, was not mandatory.

2.3. Selection criteria

The entry criteria for patients entered into this study were:

Age between 3 and 16 years inclusive, histologically proven MB, presence of leptomeningeal metastases (M2–3) on spinal MR (or myelogram in the earlier phase of the study), treated with PNET-3 CT followed by RT. Patients with metastases to the supratentorial meninges alone were classified as having M2 disease. Patients with spinal or both supratententorial and spinal metastases were classified as having M3 disease. Patients with M1 disease were included in the randomised study and therefore not included in this report. Patients treated by RT alone have been excluded from this analysis.

2.4. Surgical treatment

The maximum safe tumour resection was recommended as initial treatment. External ventricular drainage or internal CSF shunting was undertaken as deemed appropriate by the local neurosurgeon. The extent of resection was assessed by the neurosurgeon as being either a complete or less than complete resection.

2.5. Chemotherapy protocol

CT was intended to commence within 28 days of surgery. The regimen consisted of four cycles of CT at three-weekly intervals using alternating cycles of:

Vincristine 1.5 mg/m^2, days 1, 7, 14
Etoposide 100 mg/m^2, days 1, 2, 3
Carboplatin 500 mg/m^2, days 1, 2
and

Vincristine 1.5 mg/m^2, days 1, 7, 14 (day 1 only for cycle 4)
Etoposide 100 mg/m^2, days 1, 2, 3
Cyclophosphamide 1.5 g/m^2, day 1
Mesna 750 mg/m^2 was administered 15 min before and 4 and 8 h after cyclophosphamide.

2.6. Recommendations for chemotherapy dose modification

It was recommended that count recovery (total leucocyte count $> 2.5 \times 10^9$/l, neutrophils $> 1.0 \times 10^9$/l, platelets $> 100 \times 10^9$/l) should have occurred prior to the start of each cycle of CT. It was recommended that vincristine doses should be reduced or omitted for World Health Organisation (WHO) peripheral neuropathy or gastrointestinal toxicity of greater severity than grade II.

2.7. Radiotherapy protocol

Full details of the RT protocol have been reported elsewhere in Refs. [3,8]. It was recommended that RT should start as soon as possible after the last course of CT, following count recovery (neutrophils $> 1 \times 10^9$/l, platelets $> 100 \times 10^9$/l).

RT was given in daily fractions, five days per week, commencing with craniospinal RT (CSRT) and followed by a boost to the posterior fossa. The CSRT dose was 35 Gy in 21 daily fractions of 1.67 Gy. The RT dose to the posterior fossa was 20 Gy in 12 fractions of 1.67 Gy. The total RT dose to the posterior fossa was 55 Gy in 33 fractions of 1.67 Gy.

There were no general protocol recommendations for RT boosts to metastatic sites, as the original PNET-3 protocol was not designed for these patients. Whether or not to boost metastatic sites was decided by individual radiation oncologists.

2.8. Follow-up

Patients were followed up by regular clinical examination. Follow-up intervals after RT were six-weekly in the first year, three-monthly in the second year, four-monthly in the third year and six-monthly subsequently. Repeat cranial MR or CT scans were performed after CT and three months after RT. Response of leptomeningeal disease to CT was assessed from institutional reports of MR scans performed following CT. Subsequently, there were no recommendations for routine scans, and the timing of these was determined by the treating clinicians. The reporting of the pattern of relapse was based on submissions of these data on scanning by investigators. Data on the analysis of CSF samples at relapse were not requested.

2.9. Central pathology review

Central pathological review was requested for all tumours from patients entered into the study. Specimens were reviewed by two neuropathologists using the WHO classification of central nervous system (CNS) tumours [9].

2.10. Statistical methods

OS was calculated as the time from the date of diagnosis to the date of death. Patients still alive at last follow-up were censored at the date last seen. EFS was calculated as the time from the date of diagnosis to the date of first recurrence or death. In those cases where death followed recurrence, the 'event' was the recurrence. Kaplan–Meier [10] survival curves were produced and log-rank tests performed to compare OS and EFS according to possible prognostic factors. Greenwood's formula was used to calculate the standard errors, which are then used to calculate the confidence intervals (CIs).

3. Results

3.1. Patient population

Between March 1992 and January 2000, a total of 68 patients with M2–3 MB were registered with the UKCCSG and treated with CT and RT according to the PNET-3 protocol. The largest number of patients, 49 (72%), was entered from UKCCSG centres. Patients were also entered from the following countries: Denmark: 1 (2%), The Netherlands: 8 (12%), Poland: 3 (4), Spain: 7 (10%).

There were 20 (29%) males and 48 (71%) females (an unusual gender distribution), aged 2.8–16.4 years (median 7.8 years). Of the 67 patients for whom the extent of resection was known from the neurosurgical reports, 18 (27%) had complete resection, 42 (63%) less than complete resection and 7 (10%) had a biopsy only. Thirteen (19%) had Chang stage M2 and 55 (81%) stage M3 disease. Only 6 patients were able to have staging scans performed within 72 h of surgery. Only 12 patients had CSF sampling and of these 5 were positive. Fifty-seven patients (84%) had spinal staging with MR scans.

Included in this series were 9 patients who had been randomised to CT and RT in the PNET-3 study, but were later found on institutional radiology reports to have M2–3 disease. Five further patients randomised to CT and RT and excluded from the PNET-3 study and not included in this analysis included 4 with no staging scan performed and one aged less than 3 years.

The final analysis was performed in July 2004. The median follow-up is 7.2 years (range 0.1–10.9 years).

41 patients have died and 27 patients were alive at the last follow-up.

3.2. Central pathology review

MB/PNET was confirmed on central review of pathological material for 60 (88%) patients. For 5 patients pathological material was not submitted and for 3 there was insufficient material.

3.3. Compliance with the chemotherapy protocol

Most patients receiving CT, 58 (85%) received all four courses of CT. Of the 64 patients for whom details of drugs received for courses 1 and 2 were available, 59 (92%) received at least 75% of the planned CT. Of the 58 for whom details of courses 3 and 4 were available 54 (93%) received at least 75% of planned CT. For patients completing all four courses of CT, the median duration was 77 days (range 56–110 days).

3.4. Toxicity of chemotherapy

The maximum toxicities experienced by the 66 patients for whom toxicity data was received are reported in Table 1. For the 2 patients experiencing grade 3–4 renal toxicity, there was a total of 3 episodes, one each after CT course 1, 2 and 4.

There were 2 toxic deaths during PNET-3 CT. One patient died at home after a short illness with diarrhoea and poor oral intake at a time when he would have been neutropenic. One patient developed pneumonia presumed to be related to neutropenia. There was one early death due to cerebral haemorrhage, possibly related to thrombocytopenia.

3.5. Compliance with the radiotherapy protocol

Seven patients treated with CT did not receive any RT (3 died, 2 progressed, 1 parents refused, 1 unknown). The remaining 61 patients received at least RT to the posterior fossa, although one patient received only 2 Gy. A summary of RT doses delivered is given in Table 2.

Table 1
Maximum WHO grade toxicity experienced by patients throughout chemotherapy

Toxicity	WHO grade		
	0–2	3–4	Unknown
Anaemia	10 (15%)	54 (82%)	2 (3%)
Neutropenia	4 (6%)	61 (92%)	1 (2%)
Thrombocytopenia	7 (11%)	58 (88%)	1 (2%)
Gastro-intestinal	33 (50%)	29 (44%)	4 (6%)
Renal	61 (92%)	2 (3%)	3 (5%)

WHO, World Health Organisation.

Table 2
Radiotherapy doses received

	Number of patients	Median dose (Gy)	Mean dose (Gy)	Range (Gy)
Craniospinal	61	35.0	34.2	2.0–49.2
Posterior fossa	60	20.0	19.6	7.2–26.0
Metastatic boost[a]	24	48.7	47.4	40.0–55.1

[a] RT doses refer to the total dose given for metastatic disease.

3.6. Analysis of survival and event-free survival

Forty-one patients have died and 27 patients were alive at the last follow-up. There have been 5 deaths not related to relapse. In addition to the three deaths mentioned above, there was one toxic death from veno-occlusive disease with toxic encephalopathy following autologous stem cell transplantation given as second-line therapy. There was one case of secondary acute myeloid leukaemia (AML) arising 15 months after completion of therapy, with a toxic death during therapy for AML. There is no genetic information on genetic predisposition.

For all 68 patients, the OS rates were 50.0% (95% CI: 38.1–61.9%) at 3 years and 43.9% (95% CI: 32.0–55.7%) at 5 years and the EFS rates were 39.7% (95% CI: 28.1–51.3%) at 3 years and 34.7% (95% CI: 23.2–46.2%) at 5 years (Fig. 1; Table 3).

3.7. Survival according to age, gender, extent of resection, M status and treatment received

OS and EFS were compared for three age groups, 3–7 years, 8–11 years and 12–16 years. There was no significant effect of age on outcome, in relation to OS ($P = 0.27$) or EFS ($P = 0.13$).

There was no significant impact of gender on outcome, either in relation to OS ($P = 0.34$) or EFS ($P = 0.12$). Extent of tumour resection had no significant effect on OS ($P = 0.67$) or EFS ($P = 0.62$). M-Status (M2 vs M3) had no significant effect on OS ($P = 0.94$) or EFS ($P = 0.77$). The percentage of CT dose received during courses 1 and 2 had no significant effect on OS ($P = 0.82$) or EFS ($P = 0.40$), neither did the percentage CT received for courses 3 and 4 (OS: $P = 0.79$, EFS: $P = 0.54$).

For those patients who received RT, the addition of a RT boost to metastases had no significant effect on OS ($P = 0.29$) or EFS ($P = 0.73$).

3.8. Delays to radiotherapy

It was recommended that RT should be completed within 46–50 days. If completion of RT took longer than 50 days then a delay was considered to have occurred. Two patients did not complete RT as they were too ill.

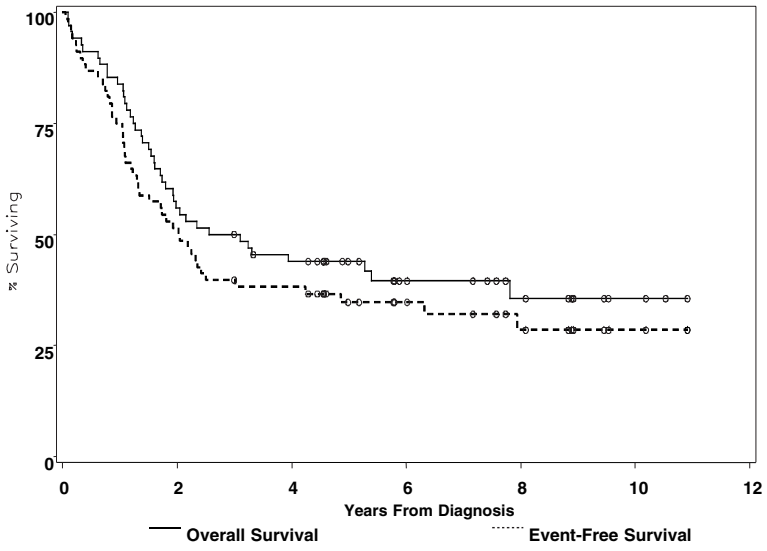

Fig. 1. Overall survival (OS) and Event-free survival (EFS).

Table 3
Comparison of outcome for M2–3 medulloblastoma in different multicentre studies

Study (with stages Included)	[Reference]	Number of patients	Dates of recruitment	Outcome at 3 years	Outcome at 5 years
SIOP II M2 + M3	[5]	29	1984–1989	EFS 43%	EFS 40%
HIT-91 M2 + M3	[6]	19	1991–1997	PFS 30%	–
CCG 921 M2 + M3 + M4	[7]	41 (M4: 2)	1986–1992	–	PFS 40%
POG 9031 M2 + M3	[14]	66	1990–1996	EFS M2: 67%, M3: 66%	–
Present study M2 + M3	This study	68	1992–2000	OS 50.0% EFS 39.7%	OS 43.9% EFS 34.7%

POG, Pediatric Oncology Group; SIOP, International Society of Pediatric Oncology; CCG, Childhood Cancer Group.

The median time taken to complete RT treatment was 47 days (range: 39–63 days). For those patients who completed RT, there was no significant difference in OS ($P = 0.52$) or EFS ($P = 0.70$) for those who completed RT within 50 days compared with those who did not.

3.9. Surgery – radiotherapy interval

For patients treated by pre-RT CT it was recommended that RT should commence within 110 days of surgery. This was not achieved for most patients. In most cases, this was due to the need for the blood count to recover following chemotherapy. The median time between surgery and RT was 117 days (mean = 121) with a range of 29–212 days. For patients completing all four courses of chemotherapy, there was no difference in OS ($P = 0.09$) for those starting RT within 110 days compared with those who started RT later than this. However, EFS was significantly worse ($P = 0.04$) for those starting RT within 110 days compared with those who started RT later than this. For patients who started RT within 110 days, EFS was 28.6% at 3 years and 23.8% at 5 years. For patients starting RT more than 110 days after surgery EFS was 52.5% at 3 years and 46.6% at 5 years. The interval between surgery and RT had no significant effect on OS ($P = 0.42$) or EFS ($P = 0.26$) when the cut-off was set at 125 days rather than 110 days.

3.10. Pattern of relapse

Of a total of 41 first relapses, 5 (12%) were local within the posterior fossa. Twenty-six (63%) were distant and 10 (24%) were combined local and distant.

3.11. Response to chemotherapy

Response to CT could be assessed from institutional radiology reports for 44 patients. Of these, 17 (39%) had a complete response (CR), 15 (34%) partial response (PR), 4 (9%) stable disease (SD), and 8 (18%) progression. The overall response rate (CR + PR) was 73%.

3.12. Survival according to response to chemotherapy

The OS at 3 years was 12.5% for those who had disease progression compared with 51.4% for those who

responded or had SD ($P = 0.002$). The EFS at 3 years was 12.5% for those who had progressive disease compared with 42.9% for those who responded or had SD ($P = 0.003$). However, these comparisons were based on small patient numbers and there was only one patient at risk in the progressive disease group.

4. Discussion

In this series, we have analysed the outcome for 68 patients with M2–3 MB treated over an eight-year period with pre-RT CT, as employed in the PNET-3 randomised study [3]. Although this was a European multicentre study, the differing accrual of patients from different national groups suggests that there may have been significant patient selection in this group of patients with M2–3 disease. Another potential bias is the fact that many patients were unable to have staging scans performed within 72 h of surgery leading to the possibility of 'over-staging' some patients.

The delivery of intensive pre-RT CT has been shown to be feasible. For these patients the median interval from surgery to RT was 117 days in this study compared with 127 days for patients treated by pre-RT CT in the randomised study [3]. EFS was significantly worse for patients commencing RT within 110 days of surgery, an effect which was lost when a cut-off of 125 days was taken. It is possible that patients commencing RT within 110 days included patients who were felt to be likely to fare less well than others.

Overall, there have been 5 deaths not related directly to MB. This proportion is higher than that seen in the randomised study, even though the same chemotherapy protocol was employed. The chemotherapy employed is myelotoxic and it is important to treat events related to myelotoxicity with caution. However, patients are being treated in the context of advanced metastatic disease with a relatively poor outlook.

Most collaborative groups have adopted risk stratification for trial entry. Patients with 'high-risk' disease include those who present with metastases (Chang stage M1–3) and those with greater than 1.5 cm^2 residual tumour on a postoperative scan.

In the last decade, the outcome for patients with 'standard-risk' MB has improved [11]. As a consequence, it has become feasible to maintain outcome, while at the same time reducing the dose of CSRT from 35–36 Gy to 23.4 Gy, hopefully reducing long-term neuropsychological morbidity [12].

Historically, the outcome for patients with Chang stage M2–3 has been poor. Most clinical trials have been directed at intensification of therapy. Direct comparison of outcomes for different series is difficult because of varying selection criteria and imaging parameters. Patients with high-risk disease with greater than 1.5 cm^2 of residual tumour on a post-operative scan are discussed in the literature, but are not included in this report. In the French M7 study which recruited between 1985 and 1988, patients with metastases had a 7-year progression-free survival (PFS) of 45% [4,13]. In the SIOP II study [5], which recruited patients between 1984 and 1989, EFS was 43% at 3 years and 40% at 5 years (Table 3). The pre-RT CT used in the SIOP II study did not result in an improved outcome and is now regarded as ineffective, and the post-RT CT for high-risk patients was limited to vincristine and CCNU. The selection criteria for this study and the SIOP II study were similar. Comparing the outcome for patients in the current study (EFS 39.7% at 3 years, 34.7% at 5 years), there has been no clear improvement compared with SIOP II. In the present study, staging MR scanning was not always performed within 24–72 h of surgery. Therefore, it is possible that there may be some patients with post-operative change rather than true M2–3 disease. It is possible that the patients with M2–3 disease treated with PNET-3 CT constituted a group with less adverse features than those in SIOP II because of the inclusion of patients with relatively small volume metastatic disease detected by MR scanning compared with the patients in the SIOP II study, the majority of whom had been staged by myelography. Despite this, the EFS for M2–3 patients in both studies was similar.

The results of the HIT-91 study [6] and the CCG 921 [8] study are given in Table 3.

The preliminary results of the POG 9031 study [14] suggest an improved outcome for patients with M2–3 MB (Table 3). This study compared pre- and post-RT cisplatin-based CT with cisplatin, etoposide, cyclophosphamide and vincristine. In this study, the same CT was employed in both arms, although the schedule was different. The CSRT dose employed for patients with M2–3 disease was 39.6 Gy. They were unable to show any significant difference in outcome with respect to the timing of CT. The preliminary outcome for M2–3 patients is better than previously reported series and further results are eagerly awaited. It is not clear whether the better outcome is due to the impact of the CT, particularly the use of cisplatin, the higher dose of CSRT employed or a combination of both. The CSRT dose of 39.6 Gy is high compared with most other series, where 35–36 Gy has been employed. What is also not yet known is the impact of the higher CSRT dose on neuropsychological outcome and endocrine function, as several studies have suggested that the degree of neuropsychological impairment is related to the CSRT dose employed [12,15]. It will be important to report the impact of this dose of CSRT on these parameters.

In the present study, patients who had disease progression during CT had a significantly worse outcome than those who had stable or responding disease. These

results have to be interpreted with caution because of small numbers of patients in the study. However, patients with disease progression during CT may in future be selected for alternative approaches, such as more intensive chemotherapy.

The finding that the outcome for M2 patients was not significantly different from M3 patients has also been found in the CCG 921 study [7]. This could be explained by the outcome being determined largely by the biological behaviour of the tumour rather than the precise extent of metastatic disease at presentation.

In the PNET-3 randomised study for M0-1 patients, those whose RT was completed within 50 days had a statistically significantly better OS and EFS than those whose RT took longer than 50 days to deliver [3,8]. OS and EFS have not been found to depend on RT duration in this study. However, the number of patients available for this analysis was much smaller than for the PNET-3 randomised study.

Although response could not be assessed for all patients, and this response assessment relied on institutional reports, most patients achieved a response to the pre-RT CT (CR: 39%, PR: 34%, SD: 9%). This is a similar finding to the pre-RT arm of the HIT-91 [7] study (Localised residual disease – CR: 57%, PR: 17%, SD 26%, Metastatic disease – CR: 42%, SD: 42%). It is important to note that patients may experience disease progression during pre-RT CT, 17% for M2–3 patients in the HIT-91 study and 18% in this study. This may be one of the reasons why pre-RT CT has not resulted in apparent improvement in outcome in this study and turned out to be inferior to immediate RT in the HIT-91 study.

The finding that patients given boosts to metastases did not have a better outcome is surprising, as patients would probably have been selected for a boost because they had relatively limited metastatic disease that could be encompassed within a boost RT field. However there were no guidelines for boost to metastases included in the protocol, and therefore this finding needs to be treated with caution.

Since RT is the main curative modality for MB and PNET, the question of whether its effects can be enhanced will be addressed in future studies. The use of carboplatin given daily as a 'radiosensitiser' is being explored for patients with high-risk PNET by the Childrens Oncology Group (COG).

There is also evidence from two studies [3,16] that prolonging RT duration for MB results in a worse outcome. The current UKCCSG study is investigating the role of Hyperfractionated Accelerated Radiotherapy (HART) [17]. The role of HART for patients with metastatic MB is also being evaluated by the Milan group, and preliminary results are encouraging with disease-free survival (DFS) rate of 78% and OS rate of 86% at 3 years [18].

In conclusion, it is not possible to make direct comparisons between patients in this study and patients with M2–3 disease in other studies because of inconsistencies in the eligibility criteria. The use of pre-RT CT appears to identify a poor prognostic group with early progression, and would permit consideration being given to the use of more intensive treatment. The future treatment of high-risk patients requires exploration of either the intensification of conventional treatments or identifying biological reasons for adverse outcomes and targeting these with specific therapies.

Conflict of interest

None declared.

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References

1. Chang CH, Housepian EM, Herbert C, *et al*. An operative staging system and a megavoltage radiotherapeutic technique for cerebellar medulloblastoma. *Radiology* 1969, **93**, 1351–1359.
2. Packer RJ, Goldwein J, Nicholson HS, *et al*. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a children's cancer group study. *J Clin Oncol* 1999, **17**, 2127–2136.
3. Taylor RE, Bailey CC, Robinson K, *et al*. Results of a randomised study of pre-radiation chemotherapy vs radiotherapy alone for non-metastatic (M0-1) medulloblastoma. The SIOP/UKCCSG PNET-3 study. *J Clin Oncol* 2003, **21**, 1581–1591.
4. Gentet J-C, Doz F, Bouffet E, *et al*. Carboplatin and VP 16 in medullblastoma: a phase II study. *Med Pediatr Oncol* 1994, **23**, 422–427.
5. Bailey CC, Gnekow A, Wellek S, *et al*. Prospective randomised trial of chemotherapy given before radiotherapy in childhood medulloblastoma. International Society of Paediatric Oncology (SIOP) and the German Society of Paediatric Oncology (GPO): SIOP II. *Med Pediatr Oncol* 1995, **2**, 166–178.
6. Kortmann R-D, Kuhl J, Timmermann B, *et al*. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomised trial HIT '91. *Int J Radiat Oncol Biol Phys* 2000, **46**, 269–279.
7. Zeltzer PM, Boyett JM, Finlay JL, *et al*. Metastasis, stage, adjuvant treatment, and residual are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. *J Clin Oncol* 1999, **17**, 832–845.
8. Taylor RE, Lucraft H, Bailey CC, *et al*. Impact of radiotherapy parameters on outcome in the International Society of Paediatric Oncology (SIOP)/United Kingdom Children's Cancer Study Group (UKCCSG) PNET-3 study of pre-radiotherapy chemotherapy for M0-1 medulloblastoma. *Int J Radiat Oncol Biol Phys* 2004, **58**, 1184–1193.
9. Kleihues PCW. *Tumors of the nervous system. World Health Organization classification of tumors*. Lyon, IARC, 2000.
10. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–482.
11. Freeman CR, Taylor RE, Kortmann RD, *et al*. Radiotherapy for medulloblastoma in children: an international perspective on current clinical research efforts. *Med Pediatr Oncol* 2002, **39**, 99–108.
12. Mulhern RK, Kepner JL, *et al*. Neuropsychologic functioning of survivors of childhood medulloblastoma randomised to receive conventional or reduced-dose craniospinal irradiation: a pediatric oncology group study. *J Clin Oncol* 1998, **16**, 1723–1728.
13. Gentet JC, Bouffet E, Doz F, *et al*. Pre-irradiation chemotherapy including 'eight drugs in 1 day' regimen and high-dose methotrexate in childhood medulloblastoma: results of the M7 French Cooperative Study. *J Neurosurg* 1995, **82**, 608–614.
14. Tarbell NJ, Friedman H, Kepner J, *et al*. Outcome for children with high stage medulloblastoma: results of the Pediatric Oncology Group 9031 study. *Int J Radiat Oncol Biol Phys* 2000, **48**(Suppl.), 179.
15. Grill J, Kieffer Renaux V, Bulteau C, *et al*. Long-term intellectual outcome in children with posterior fossas according to radiation doses and volumes. *Int J Radiat Oncol Biol Phys* 1999, **45**, 137–145.
16. del-Charco JO, Bolek TW, McCollough WM, *et al*. Medulloblastoma: time–dose relationship based on a 30-year review. *Int J of Radiat Oncol Biol Phys* 1998, **42**, 147–154.
17. Wheldon TE, O'Donoghue JA, Barrett A. Kinetic considerations in the choice of treatment schedules for neuraxis radiotherapy. *Br J Radiol* 1993, **66**, 61–66.
18. Gandola L, Cefalo G, Massimino M, *et al*. Hyperfractionated accelerated radiotherapy (HART) for metastatic medulloblastoma. *Neuro-Oncology* 2003, **5**, 39–40.