Chemotherapy Dose-intensity and Survival for Childhood Medulloblastoma

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Abstract. *Aim: To determine the relationship between prescribed dose-intensity of chemotherapy and survival in childhood medulloblastoma. Materials and Methods: A total of 55 trials from 1970-2009 were identified, 30 were eligible for analysis, with individual treatment regimes with 5-year (or more) outcome figures. Relationships of outcome to dose-intensity were analysed using weighted regression. Results: Overall, 2,434 patients were identified, 1,010 were classified as 'standard'- and 671 as 'high'-risk patients, with 5-year overall survivals (OS) of 67.2% (95% Confidence Interval=60.5%-73.6%) and 47.6% (95% Confidence Interval=39.5%-55.7%), respectively. A protective effect for chemotherapy versus craniospinal radiotherapy alone (5-year OS of 58.2% versus 51.6%) was found. Individually, vincristine, cisplatin, lomustine (CCNU) and cyclophosphamide appear to confer the most beneficial effect, particularly for high-risk patients. Positive relationships between OS and dose-intensity were found, except for lomustine, with cyclophosphamide offering the greatest protection. Conclusion: Consideration of chemotherapy dose-intensity may further optimise treatment, particularly in the context of risk stratification.*

Cancer is rare among children, with one in 500 children in the western world developing cancer before aged 15 (1). Tumours of the central nervous system (CNS) are the second most common form of childhood cancer, following haematological malignancies, and are the leading cause of cancer-related illness and death in children (2). Medulloblastoma accounts for 20% of CNS tumours and 40% of cerebellar tumours, affecting 1 per 200,000 children each year (2, 3), with a peak incidence for diagnosis occurring between 4-9 years of age (2). The prognosis for medulloblastoma is largely effected by the extent of surgical resection (residual disease), tumour dissemination and age. As such, patients are now classified as having standard-risk or high-risk disease.

Currently a combination of surgery, radiotherapy and chemotherapy is used to treat medulloblastoma. For high-risk patients, a standard dose of 35-36 Gy of radiotherapy is usually given to the craniospinal axis followed by a boost to the entire posterior fossa [total dose of 54-55 Gy (4)]. For standard-risk patients however, attempts at reducing the neuropsychological sequelae of treatment have been made by reducing the radiotherapy dose to 23.4 Gy, to the craniospinal axis. However, without adjuvant chemotherapy, reduced-dose radiotherapy is associated with poorer survival (5).

Whilst many chemotherapy agents have been employed in the treatment of medulloblastoma, many contemporary chemotherapy protocols include use of a combination of agents from cisplatin, carboplatin, vincristine, lomustine (CCNU) and cylophosphamide (6, 7). However, there is a large variation in the dose-intensity given of these individual drugs that can arise as a function of the protocol employed, or due to dose or drug modifications that are mandated as a response to toxicity (8).

The dose-intensity of chemotherapy (both prescribed and received) has been found to have an impact on the survival for many different types of childhood cancer, including neuroblastoma (9), ependymoma (10) and acute lymphoblastic leukemia (11). Such a relationship has not been investigated in the setting of childhood medulloblastoma. Therefore, the aim of this study was to investigate the potential importance of dose-intensity as a determinant of the additional benefit conferred by chemotherapy when compared with radiotherapy-alone, both overall and in the context of patient risk factor and radiotherapy dose.

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Materials and Methods

Patients and treatment protocols. Medline, Embase and Cochrane Libraries were searched to identify all up-front phase III clinical trials (from August 1970 to February 2009) for the treatment for children and adolescents (aged 0 to 18 years) with medulloblastoma [or Primitive Neuroectodermal Tumour (PNET), if not specified]. Fifty-five trials were identified, and 30 of these were eligible for inclusion in the patient database. Eligible articles included only those reporting individual treatment regimes with identifiable 5-year or more outcome figures [either overall survival (OS), event-free survival (EFS), or progression-free survival (PFS)] and a uniform radiotherapy dose to the craniospinal axis.

This resulted in a patient database of 2,434 patients from 30 clinical trials (5, 6, 12, 13-39). Out of these, eight trials included patients treated with radiotherapy alone (22, 24, 28, 30, 34, 36, 37, 39) (380 patients) and two trials of patients treated with chemotherapy alone (16, 20) (64 patients).

The number of patients undergoing reduced-dose radiotherapy (18-25 Gy to the craniospinal axis) was 607 [included in eight trials (6, 13, 15, 21, 25, 29, 33, 39)] and 1,763 patients underwent standard-dose radiotherapy (30-40 Gy to the craniospinal axis) [from 24 trials (7, 12, 13-15, 17-19, 22-24, 26-28, 28-39)].

High-risk patients (n=671) (7, 13-16, 18-21, 22, 26, 28-31, 33-38) were either defined by the publication of origin or if the patient had either a subtotal resection of the tumor (>1.5 cm^2 of residual tumor), was aged under 3 years at diagnosis, or had disseminated disease. Patients with disseminated disease were defined as those patients with either microscopic tumor cells found in the cerebral spinal fluid (CSF) [M1 of the modified Chang staging system (40)], metastatic disease on neuroimaging (M2-3), or extraneural metastasis (M4) (3, 40). Standard-risk patients (n=1,010) (6, 13-15, 19, 24-26, 28, 30, 31, 36, 39) were simply defined as all other patients not included in the above definition. For the remainder of the patients (n=746) (12, 17, 21-23, 26, 29, 32-34, 37, 38), it was not possible to ascertain risk status from the publication of origin.
For the purposes of analysis the following categories of patients were defined: i. High-risk patients undergoing radiotherapy-alone (n=34) (34, 36); ii) standard-risk patients undergoing radiotherapy-alone (n=227) (24, 28, 30, 36, 39); iii) high-risk patients undergoing some form of chemotherapy (n=637) (7, 13-16, 18, 19, 24, 26, 28, 30, 31, 33-36, 38); iv) standard-risk patients undergoing some form of chemotherapy (n=790) (6, 13-15, 19, 25, 26, 30, 31, 36); v) patients undergoing chemotherapy and reduced-dose radiotherapy (n=567) (6, 13, 15-19); vi) patients undergoing chemotherapy and standard-dose radiotherapy (n=1,423) (6, 12, 13-15, 17-19, 22-26, 28, 30, 31, 33-38); vii) standard-risk patients undergoing chemotherapy and reduced-dose radiotherapy (n=542) (6, 7, 13, 15, 17-19); viii) standard-risk patients undergoing chemotherapy and standard-dose radiotherapy (n=248) (6, 14, 15, 22, 24, 31); ix) high-risk patients undergoing chemotherapy and reduced-dose radiotherapy (n=15) (7, 15, 17, 19); and x) high-risk patients undergoing chemotherapy and standard-dose radiotherapy (n=558) (6, 12, 13-15, 17, 18, 22-24, 28, 30, 33, 34, 37, 38)

Outcome. For inclusion in the database, trials had to identify outcome measures for each treatment protocol used. Publications detailing a combination of several protocols, with only one combined outcome measure were considered unacceptable for inclusion.

The outcome measure used, where possible, was OS at 5 years. Five-year EFS and PFS were used where OS was unavailable. In addition, any of these outcome measures quoted for periods longer than 5 years was used when the 5-year figure was not quoted. Any outcome measure under 5 years was excluded.

Analysis. Survival rate outcome: Patients' 5-year survival rates were analysed using a weighted least square regression model to investigate how the survival rate is influenced for childhood medulloblastoma. R(42) was used to perform meta-analysis techniques, allowing for random effects (Der Simonian-Laird) to combine the outcome measures of all the individual studies/patients. This also returned the 95% confidence intervals (CI) detailed.

To compare the effect of chemotherapy versus radiotherapy alone, statistical significance testing was carried out in R, for a 95% CI.
Dose intensity: The calculation for dose-intensity was made by the summation of the total dose over the entire treatment plan divided by the total number of weeks from chemotherapy commencement, to the week for which the last chemotherapy agent in the regimen was prescribed. The duration of radiotherapy was assumed to be six weeks unless specified otherwise. Where doses were not recorded in mg/m^2, doses were converted using age-related averages as detailed in the British National Formulae for children (43).

When analysing dose-intensity for individual drugs, outcome (survival at 5 years) was calculated using a cumulative method (*i.e.* meta-analysis allowing for random effects was not used). This calculation was carried out by multiplying the outcome for each individual study/category by the number of patients in each study/category. This was then combined by a simple summation. To measure the additional benefit conferred by chemotherapy or the individual agents studied, regression analysis was carried out using weighted regression (weighted by the number of patients in each study).
Relative risk: The risk of any treatment regime or chemotherapy agent was calculated as 1 minus the outcome figure for that treatment, expressed as a proportion of 1, so that a survival of 68% equals 0.32. [interpreted as the risk of not surviving (dying) over the 5-year period]. Thus, relative risk was calculated as the risk (probability of death) of that treatment divided by the figure for the risk (probability of death) of the directly comparable radiotherapy-alone. For example, relative risk for standard-risk patients undergoing some form of chemotherapy was calculated by the probability of death over the 5-year period for all standard-risk patients undergoing chemotherapy (6, 13-15, 19, 25, 26, 30, 31, 36) divided by the probability of death over the 5-year period for all standard-risk patients undergoing radiotherapy alone (24, 28, 30, 36, 39).
Radiotherapy dose: For the purpose of the analysis, the cut-off for reduced-dose radiotherapy was 24.6 Gy or below, whilst all other doses were classified as standard radiotherapy.

Results

The 5-year survival rate (OS+EFS+PFS) for the 2,434 patients identified was 56.9%. Out of these, 1,017 were classified as 'standard'-risk and 671 as 'high'-risk patients, with an associated 5-year OS of 67.2% (CI=60.5%-73.6%) and 47.6% (CI=39.5%-55.7%), respectively.

Overall, a protective effect of chemotherapy was found. For the whole study population, 5-year survival for those

Table I. *The 5-year survival rates (together with the confidence interval of this figure) for the various combinations of patient risk factors, treatment modality and the radiotherapy dose received.*

Treatment received and patient category	Number of patients (n)	5-Year overall survival (%)	95% Confidence interval (%)
Total study	2,434	56.9	52.3-61.5
RTX-alone	380	51.6	41.8-61.2
CTX	2,054	58.2	53.0-63.3
High-risk patients	671	47.6	39.5-55.7
Standard-risk patients	1,010	67.2	60.5-73.6
RTX-alone and high-risk patients	34	23.1	3.2-85.6
RTX-alone and standard-risk patients	227	58.0	49.3-66.4
CTX and high-risk	637	49.3	41.3-57.3
CTX and standard-risk	790	73.1	66.0 – 79.7
CTX and reduced RTX	567	83.1	79.8 – 86.2
CTX and standard RTX	1,423	54.8	49.9 – 59.6
CTX, standard-risk and reduced RTX	542	83.6	79.5- 87.3
CTX, standard-risk and standard RTX	248	65.2	56.6-73.3
CTX, high-risk patients and reduced RTX	15	72.7	55.7-86.9
CTX, high-risk patients and standard RTX	558	46.2	37.9-54.6

CTX, Chemotherapy; RTX, radiotherapy.

patients undergoing radiotherapy alone was 51.6%, whilst that of patients given some form of chemotherapy (N=1990) was 58.2% (p=0.003).

For survival at 5 years, the combination of patient risk factor, treatment modality and the radiotherapy dose received was examined, both individually and in combination (Table I). Overall, chemotherapy administered during and after radiotherapy was more effective than pre-radiotherapy treatment, with 5-year survival figures for the total population of 69.1% and 60.7%, respectively.

The impact of individual drugs on 5-year survival. Where a protocol contained a specific drug, survival data were recorded and combined with all other protocols containing that drug. Individually, treatment with any of the four most commonly employed chemotherapy agents of vincristine, cisplatin, CCNU and cyclophosphamide appear to be amongst the most beneficial compared to radiotherapy-alone. With vincristine and cisplatin having the lower 95% confidence level above the survival rate of radiotherapy-alone (51.6%) and CCNU and cyclophosphamide only marginally below (49.6% and 51.3%, respectively). In addition, both etoposide and methotrexate also have a lower 95% confidence level above the survival rate of radiotherapy-alone (Figure 1).

Chemotherapy dose-intensity and 5-year survival. The prescribed dose intensities for vincristine, cisplatin, CCNU and cyclophosphamide varied considerably between individual treatment regimens. For example, whereas there is at least almost a 5-fold range for vincristine and cisplatin dose-intensities between published treatment protocols, the variation for cyclophosphamide is even greater (almost 10-fold). With respect to the chemotherapy agents vincristine, cisplatin and cyclophosphamide, a positive relationship between survival and dose-intensity was found (cyclophosphamide is shown in Figure 2 as an example).

For cyclophosphamide, each mg/m^2/week increase in dose intensity results in an increase in the weighted survival rate by 0.06% (with an adjusted R^2 value of 26.39%). For vincristine and cisplatin, the equivalent survival rate increase is 20.7% and 0.1% (with adjusted R^2 values of 12.5% and 7.8%, respectively), whilst for CCNU, each mg/m^2/week increase in dose intensity results in an apparent decrease in survival of 0.19% (adjusted R^2 of –3%).

Chemotherapy dose-intensity and relative risk (additional benefit to that of radiotherapy given alone). When compared to radiotherapy-alone, even the minimum doses used in any of the protocols examined of vincristine, cisplatin, cyclophosphamide and CCNU provide benefit relative to

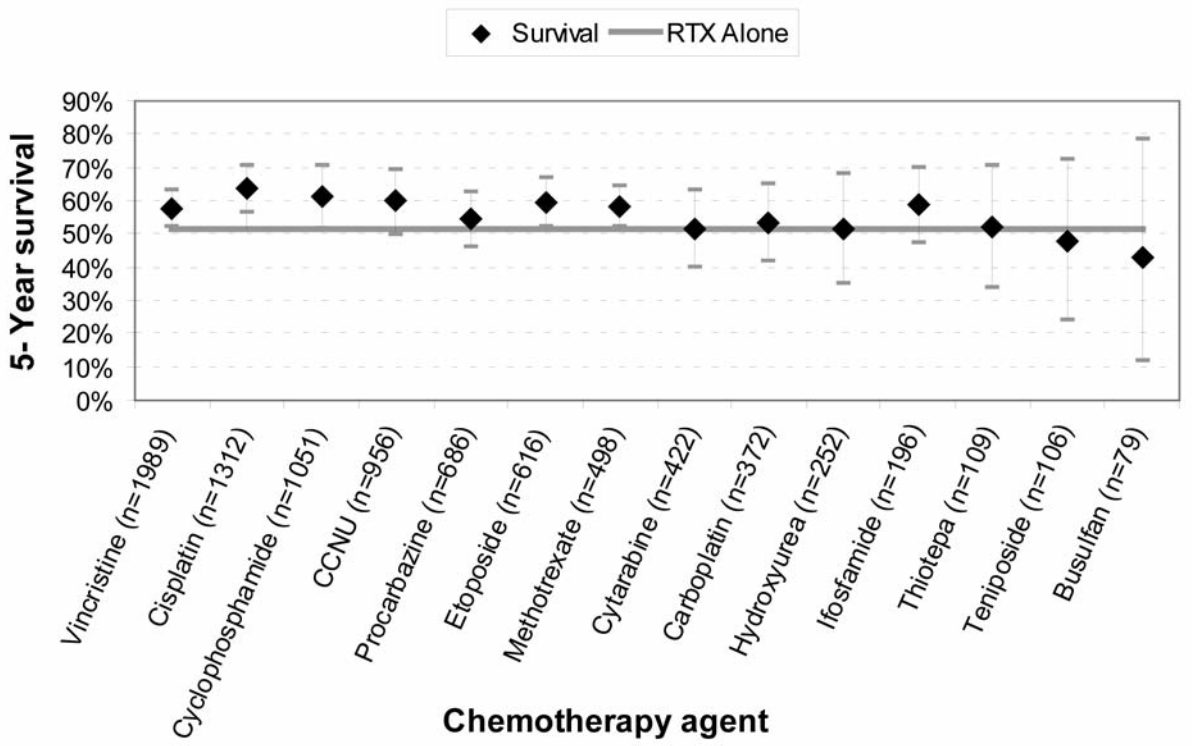

Figure 1. *Box plots (including confidence intervals) of the 5-year survival for the various chemotherapy agents that have been employed in treatment protocols for children with newly-diagnosed medulloblastoma. The 5-year survival rate of patients undergoing radiotherapy-alone is also shown. Where a protocol contained a specific drug, survival data were recorded and combined with all other protocols containing that drug. N, number of patients receiving that agent; CCNU, lomustine; RTX, radiotherapy; bars indicate the 95% confidence interval.*

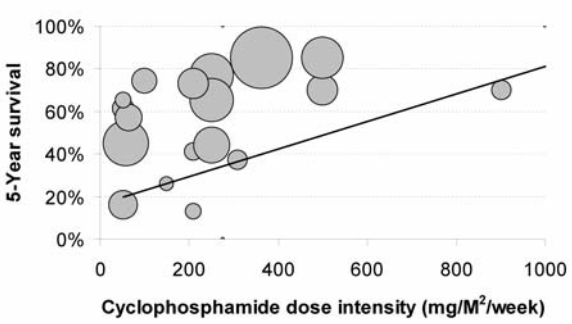

Figure 2. *A bubble chart showing the positive relationship between the prescribed dose intensity of cyclophosphamide and 5-year overall survival for all patients where cyclophosphamide is included in the treatment regime. The area of the plots represents the number of patients in a particular study. The regression line and adjusted R^2 are weighted by the number of patients in each study. The adjusted R^2 value is 26.4%.*

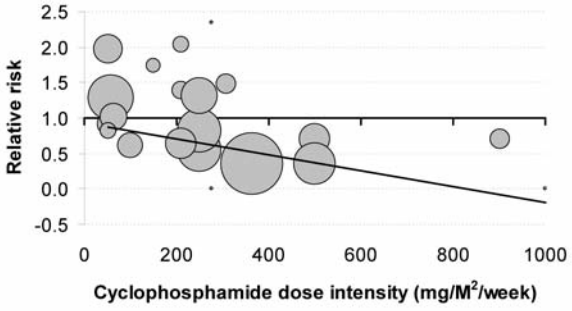

Figure 3. *This bubble chart shows the relationship between the prescribed dose intensity of cyclophosphamide and the relative risk of death for radiotherapy-alone, for all patients where cyclophosphamide is included in the treatment regime. The area of the plots represents the number of patients in a particular study. The regression line and adjusted R^2 are weighted by the number of patients in each study. The adjusted R^2 is 26.4%.*

radiotherapy-alone. However, this relative benefit appears to increase as the dose-intensity increases for all except CCNU, where the benefit largely remains stable irrespectively of dose. The data plots for cyclophosphamide are shown as an example (Figure 3).

Chemotherapy dose-intensity and relative risk of death (additional benefit over radiotherapy given alone) according to patient risk. The results of weighted-regression analysis of the relationship between OS and dose-intensity for vincristine, cisplatin, cyclophosphamide and CCNU are

Table II. *Weighted regression analysis of the relative risk of death (versus radiotherapy alone) for various patient risk categories as a function of the dose-intensity of vincristine, cisplatin, cyclophosphamide and lomustine (CCNU).*

Chemotherapy agent	Analysis	Relative risk		
		All patients	Standard-risk patients	High-risk patients
Vincristine	Regression	Y=–0.3604x+0.8839	Y=0.0618x+0.2930	Y=–0.2807x+1.0086
	Adjusted R^2	12.48%	1.00%	2.00%
Cisplatin	Regression	Y=–0.0174x+0.7719	Y=–0.0202x+0.5922	Y=–0.0323x+1.1906
	Adjusted R^2	7.80%	22.19%	15.40%
Cyclophosphamide	Regression	Y=–0.0011x+0.9352	Y= – 0.0007x+0.5529	Y=–0.0008x+1.1698
	Adjusted R^2	26.39%	68.29%	25.43%
CCNU	Regression	Y=–0.0033x+0.5584	Y=–0.0049x + 0.4309	Y=0.0194x+0.5735
	Adjusted R^2	–3.00%	–31.00%	–7.00%

shown in Table II. For all standard-risk patients receiving treatment containing any of vincristine, CCNU, or cyclophosphamide, a positive effect of dose intensity on survival is found across the range of dose-intensities described in the literature. This effect is stronger for cyclophosphamide and cisplatin, and weaker for vincristine. Of particular note is the adjusted R^2 of 68.29% for standard-risk patients receiving cyclophosphamide, showing the strength of the negative relationship between dose-intensity and relative risk. However, for CCNU, increasing the dose intensity relates to an adverse outcome.

For high-risk patients, the protective effect of the individual chemotherapy agents is still in the order cyclophosphamide >cisplatin>vincristine, but the effect of dose intensity is less pronounced than for standard-risk patients. Once again-however, there is a negative relationship between CCNU dose-intensity and OS.

Discussion

Chemotherapy is now an accepted component of the treatment for childhood medulloblastoma and with current practice, this modality generally follows radiotherapy to the CNS axis. However, contemporary protocols have a large variability for prescribed and received chemotherapy dose-intensity (8). Therefore, the aim of this investigation was to look for evidence for any importance of the prescribed dose intensity for those chemotherapy agents that are employed for the therapy of childhood medulloblastoma, both overall and in the context of certain risk factors for recurrence.

Radiotherapy forms the mainstay of therapy for medulloblastoma. Our analysis revealed that the 5-year survival for the total patient population studied was 52% for all those undergoing radiotherapy-alone, and radiotherapy alone was less protective for those patients with high-risk disease by a factor of three-fold in comparison to children with standard-risk disease.

In addition, our analysis demonstrates that chemotherapy appears to add to the benefit of radiotherapy, and overall, our study reveals a significant improvement of nearly 7% in the 5-year OS for those patients undergoing chemotherapy when compared to the expected survival with radiotherapy alone.

Whilst examining the effect of chemotherapy in the context of radiotherapy dose, the 5-year survival for patients who received reduced doses of radiotherapy were better than those receiving standard radiotherapy doses, and this effect was seen irrespective of risk-factor grouping. However, chemotherapy and reduced-dose radiotherapy mainly utilised those drugs that seem to confer the most benefit in the context of medulloblastoma therapy, namely vincristine, cisplatin, CCNU and cyclophosphamide. In particular, 80% of the combined chemotherapy and reduced-dose patients group are from the contemporary studies reported by Packer and colleagues, where 5-year survival figures are generally in excess of 80% for standard-risk patients (6, 25, 33).

Analysis of the protective effect that is conferred by the individual chemotherapy agents employed in up-front clinical trials, to date, for children with medulloblastoma indicate the potential importance of vincristine, CCNU, cisplatin and cyclophosphamide as individual components of therapy. Therefore, we investigated if there were any evidence for the relative importance of prescribed dose-intensity and found that considerable variation exists between the individual trials reported in the literature. The importance of chemotherapy dose-intensity has been described for a variety of other types of pediatric cancer, both for prescribed dose-intensity and received dose-intensity. For example, increasing the prescribed dose-intensity of cisplatin, vincristine, carboplatin, etoposide and cyclophosphamide has improved survival for children with high-risk neuroblastoma (44) and the received dose intensity in a chemotherapy regimen for infants with ependymoma relates significantly to survival (9).

For all patients with medulloblastoma in our analysis, a positive relationship between dose-intensity and outcome in

terms of 5-year OS was found for cyclophosphamide and cisplatin, and a very weak one for vincristine. For CCNU, a negative relationship between dose-intensity and outcome was described, and these relationships were larger in the setting of standard-risk disease when compared with high-risk disease. However, the relationship between survival and dose-intensity was most significant for cyclophosphamide in the context of children with standard-risk disease. This phenomenon may explain, at least in part, the success of chemotherapy regimens containing higher doses of cyclophosphamide in the therapy of high-risk disease, where the dose intensity of 500 mg/m^2/week lies towards the upper end of the range of dose intensities reported to date (13).

If prescribed chemotherapy dose-intensity is an important determinant of outcome for childhood medulloblastoma, then received dose-intensity may also be of concern. Indeed, current protocols promote a level of heterogeneity with respect to the dose-intensity received of a particular chemotherapy agent. Current UK practice recommends that cisplatin is replaced by carboplatin in the face of a predetermined level of oto- or nephrotoxicty. An analysis of the actual received dose-intensity that results from this practice revealed that only two-thirds of patients achieved vincristine and CCNU dose-intensities of greater than 90% of the intended doses, and only one-tenth of children achieved this level of dose-intensity with cisplatin (8).

In conclusion, chemotherapy is now an established modality for the therapy of childhood medulloblastoma. However, our study shows that except for the case of CCNU, the prescribed dose-intensity, particularly for cyclophosphamide in the setting of standard-risk disease, has a favourable impact on prognostic significance. Further studies are needed to determine the relationship between received dose-intensity and outcome in childhood medulloblastoma, which may in turn help in the rational development of chemotherapy protocols that optimise the chemotherapy and radiotherapy burden for the different risk settings for this disease.

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