

## The Prognostic Impact of Additional Chemotherapy to Radiation Therapy for Postoperative Management of Pediatric Medulloblastoma

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### ABSTRACT

**Purpose:** The aim of this study is to evaluate treatment results of combined therapy; surgery, postoperative craniospinal radiotherapy with chemotherapy compared to treatment with postoperative radiotherapy only. Also to assess the effect of extent of surgical resection on prognosis.

**Patients and Methods:** Between 1993 and 2003, 34 children >3 years of age with nondisseminated medulloblastoma were treated with postoperative, craniospinal radiation therapy (36 Gy in 20 fractions to the craniospinal axis, supplemented by a posterior fossa dose of 1980 cGy in 11 fractions (total dose of 56 Gy). Daily fractions of 1.8 Gy were used. Out of them, 16 children received chemotherapy in the form of vincristine, at a dose of 1.5mg/m<sup>2</sup>, which was given weekly during radiotherapy. One month after completion of radiation therapy, chemotherapy was continued every 4 weeks with cycles of cyclophosphamide (750mg/m<sup>2</sup>) and vincristine(2mg/m<sup>2</sup>) for a maximum dose of 2mg, alternating with vincristine and carboplatin (500mg/m<sup>2</sup>). A total of 12 alternating cycles were administered.

**Results:** The follow-up period ranged from 14-132 months. The median overall survival (OAS) for the whole group was 49.5 months (mean of 61±38) while the median progression free survival (PFS) was 47.5 months (mean 59.6±39). Although both PFS and OAS were better among those who had total resection than subtotal resection (estimated 5-y PFS of 60% and 64% for both groups, respectively and estimated 5-y OAS of 65% for subtotal resection and 69% for those underwent total resection), however this difference was not statistically significant ( $p=0.1$ ). The median PFS for the chemotherapy group was 60.5 months (Mean was 72.6±41.7) while that for the non-chemotherapy group was 39.5 months (mean 48±33.6). The difference was of borderline significance with a  $p$ -value of 0.06. The estimated 5-year progression free survival for the chemotherapy group was 70% while that of no chemotherapy group was 59% with a  $p$ -value of 0.25. While the estimated 5-year overall survival for chemotherapy group was 70% in comparison to 60% for

non-chemotherapy group giving borderline statistical significance difference with a  $p$ -value of 0.8.

**Conclusion:** Maximum possible surgical resection, postoperative radiotherapy and adjuvant chemotherapy are important factors in improving outcome in the management of medulloblastoma.

**Key Words:** Medulloblastoma - Chemo-radiotherapy - Prognostic factors.

### INTRODUCTION

Medulloblastoma is the most common malignant brain tumor of childhood, accounting for approximately 20 percent of all primary tumors of the central nervous system among children less than 19 years old [1,2].

At present, children with medulloblastoma are divided into two disease risk groups [3,4]: Average-risk patients: are those diagnosed when they are older than the age of 3 years with nonmetastatic and totally or near-totally resected disease ( $\leq 1.5$ cm) on postoperative magnetic resonance imaging [MRI] and or CT scan; patients not fulfilling these criteria are regarded as high-risk.

Until approximately the late 1980s the conventional treatment of children with medulloblastoma after surgery consists of 36 Gy of craniospinal irradiation supplemented with 18 to 20 Gy of local irradiation (total dose to posterior fossa of 54 to 56 Gy) [5]. Using this approach, a 5-year survival rate of 60-65% was achieved [6].

Several randomized studies have evaluated the contribution of adjuvant chemotherapy, most

often CCNU (lomustine), vincristine, and cisplatin, following surgical resection [7,8]. Benefit has been demonstrated most convincingly in patients with high-risk disease, and has been limited to better event-free but not overall survival [9,10].

This report evaluates the experience of King Abdulaziz Hospital and Oncology center, Jeddah, Saudi Arabia, in treating medulloblastoma and the effect of using immediate postoperative radiotherapy with concomitant and adjuvant chemotherapy.

### PATIENTS AND METHODS

Between 1993 and 2003, 34 children >3 years old, at the time of diagnosis, with medulloblastomas were eligible for analysis. Pathology for all the patients was revised in our center to confirm the diagnosis of medulloblastoma. Postoperative CT scan and/or magnetic resonance imaging (MRI) of the entire brain and spine, and CSF cytologic examination were performed for all the patients. Both studies were repeated 4 weeks post radiotherapy and prior to chemotherapy then repeated again 6, 12, 24 months from the start of chemotherapy. After these assessments, patients were designated a T-stage according to Chang staging system for posterior fossa medulloblastomas [11,12].

The degree of tumor resection was determined by the postoperative images and the surgeon's impression at the time of completion of surgery. Tumor resections were graded as total resection (no areas of residual disease), subtotal (>90% of the tumor was removed) or otherwise considered as biopsy. If tumor was not visible on the postoperative image, but the surgeon believed the tumor was incompletely resected, the degree of surgery was considered incomplete. All patients were considered eligible regardless of the degree of tumor resection.

#### *Treatment Protocol:*

All patients received 36 Gy in 20 fractions to the craniospinal axis, supplemented by a local tumor dose of 1980 cGy in 11 fractions (total dose of 56 Gy). Daily fractions of 1.8 Gy were used. Those who received chemotherapy, vincristine, at a dose of 1.5mg/m<sup>2</sup>, was given weekly during radiotherapy. One month after completion of radiation therapy, chemotherapy was continued every 4 week with cycles of

cyclophosphamide (750mg/m<sup>2</sup>) and vincristine (2mg/m<sup>2</sup>) for a maximum dose of 2mg, alternating with vincristine and carboplatin (500mg/m<sup>2</sup>). A total of 12 alternating cycles were administered.

Craniospinal irradiation (CSRT) was performed in the prone position using parallel-opposed lateral cranial fields that abutted a posterior spinal field [13]. In older children, upper and lower spinal fields separated by a skin gap were used. The initial craniospinal junction was set low, just above the shoulders to avoid exit of radiation to the thyroid gland from the posterior spinal field, junctions were changed every five treatments [14]. Usually, the cranial field length was decreased, whereas the spinal field length was increased with an upward shift of the spinal isocenter. If there were two spinal fields, the upper field length stayed the same, whereas the lower field length was increased; both spinal isocenters were shifted superiorly with the corresponding skin gap. It is therefore possible for the thyroid gland to get exit dose from the spine field with a new junction change, even if the original spinal field did not exit or diverge into the thyroid gland [13].

#### *Statistical Analysis:*

Statistical analysis was performed using SPSS 10.0 software. Progression free survival (PFS) was calculated from the day of surgical interference till the last event. Overall survival (OAS) was calculated from the first day of treatment to the last follow-up date or death.

Paired *t*-test was used to compare mean variables,  $\chi^2$  test to compare percentages, and Kaplan-Meier method was used to calculate survival curves [15].

### RESULTS

Thirty-four patients were found to be eligible for this analysis. Twenty-four patients were males and 10 were females with a male to female ratio of about 2:1. The age of the whole group ranged between 3.5 years to 20 with a mean of 9.2 and median of 8.5 years. Extent of tumor at the time of diagnosis, as designated by T-stage, was T2 in 8 patients, T3 in 16 patients, and T4 in 10 patients. Twenty-four patients were staged as M0, 10 were of M1 stage.

The maximum follow-up period was 132 months while the minimum was 14 months. The median OAS for the whole group was 49.5 months (mean of 61±38) while the median PFS was 47.5 months (mean 59.6±39).

Five patients had biopsy only. Subtotal resection (>90%) was performed for 16 patients while the rest underwent total resection. Three

of the 5 biopsy-only patients received radiotherapy only and they didn't enter in complete remission and the three died with the disease. The other two patients received the full protocol of chemotherapy and radiotherapy. The MRI after radiotherapy showed CR, both were of stage T2 M0 and both were still alive free of disease with a follow-up period of 24 months.

Table (1): Effect of the extent of surgical resection.

Extent of surgery	No of Patients	PFS			OAS		
		Mean (months)	Median (months)	<i>p</i> -value	Mean (months)	Median (months)	<i>p</i> -value
Total	13	76.0	77.5	0.125	76.3	77.5	0.119
Sub total	16	53.8	47.0		54.0	47.0	
Biopsy	5	22.0	24.0		29.6	24.0	
All	34	59.0	47.5		60.9	49.5	

Both PFS and OAS were better among those who had total resection rather than subtotal resection. The median PFS for those with subtotal resection was 47 months (mean 53.8±33) in comparison to 77.5 months (mean 76±40) for those who underwent total resection, with

more or less the same figures for OAS (Table 1), however this difference was not statistically significant (*p*=0.1). Estimated 5-y PFS for both groups was 60%-62%, and estimated 5-y OAS for subtotal resection group was 65% and 69% for those undergone total resection. (Figs. 1,2).

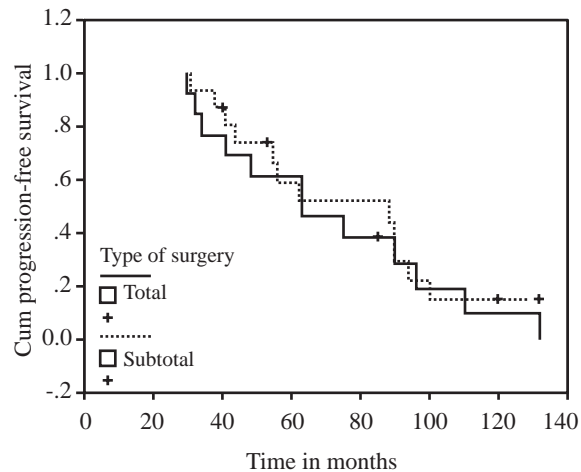


Fig. (1): Kaplan Meier progression free survival of medulloblastoma patients in relation to the extent of surgery.

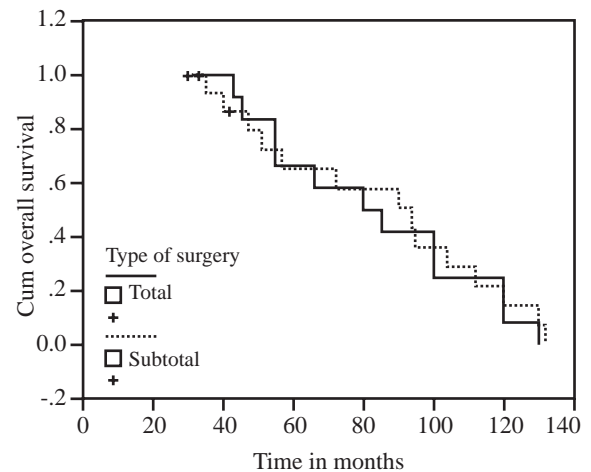


Fig. (2): Kaplan meier overall survival of medulloblastoma patients in relation to the extent of surgery.

Only sixteen of the 34 patients received chemotherapy. The OAS and PFS for them were much higher than those of the non-chemotherapy group. The median PFS for the chemotherapy group was 60.5 months (Mean was 72.6±41.7) while that for the non-chemotherapy group was 39.5 months (mean 48±33.6). The difference was of borderline significance with a *p*-value

of 0.06 (Table 2). The estimated 5-year progression free survival for the chemotherapy group was 70% while that of no chemotherapy group was 59% with a statistically significant difference (*p*-value of 0.025) (Fig. 3).

The median OAS for the chemotherapy group was 60.5 months (mean 73±41.42) while that of the non-chemotherapy group was 44

months (mean  $50.2 \pm 32.4$ ) with a  $p$ -value of 0.08 (Table 2). While the estimated 5-year overall survival for chemotherapy group was

70% that of non-chemotherapy group was 60% giving borderline statistically significant difference with a  $p$ -value of 0.08 (Fig. 4).

Table (2): Influence of chemotherapy treatment with the radiotherapy on the survival of medulloblastoma patients.

Extent of surgery	No of Patients	PFS			OAS		
		Mean (months)	Median (months)	$p$ -value	Mean (months)	Median (months)	$p$ -value
Chem. group	16	72.6	60.5	0.06	73.0	60.5	0.08
Non-chem. group	18	48.0	39.5		50.2	44.0	
All patients	34	59.5	47.5		60.9	49.5	

Chem. = Chemotherapy.

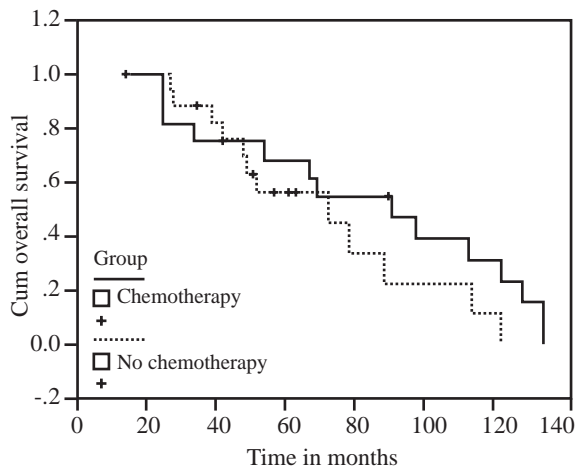


Fig. (3): Kaplan Meier Progression free survival of Medulloblastoma patients in relation to chemotherapy administration.

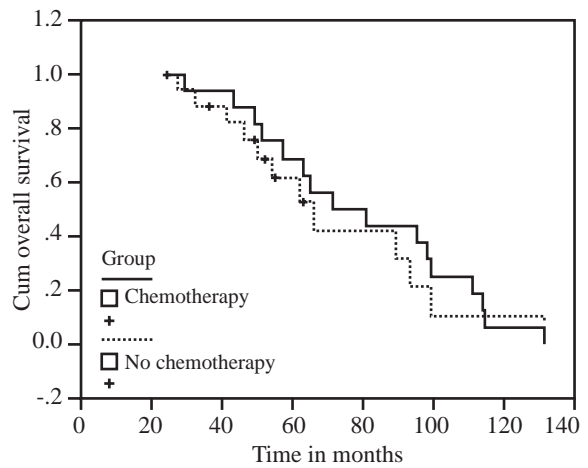


Fig. (4): Kaplan Meier Overall survival of Medulloblastoma patients in relation to chemotherapy administration.

### DISCUSSION

Several strategies have been used in an attempt to improve survival and decrease the long-term consequences of treatment of medulloblastoma. One strategy was to decrease the CSRT dose delivered to 23.4 Gy while maintaining the same dose (54-55.8 Gy) to the posterior fossa. A second approach was to incorporate chemotherapy into the treatment regimen. Trials using chemotherapy were initiated in the late 1980s and early 1990s. Our study was incorporated to evaluate the effect of adding chemotherapy to classic radiotherapy treatment in King Abdulaziz Hospital and Oncology center.

There is increasing agreement in the literature about the importance of surgical resection in this disease. Although, resectability rates

vary from 40-70%, the more important variable appears to be the degree of post-operative residual. One of the conclusions of the Children's Cancer Group 921 trial, addressing the relative efficacy of two different chemotherapy regimens along with standard radiotherapy doses, was the adverse effect of a residual  $>1.5\text{cm}^2$  in patients more than 3 years of age and with M0 disease [16].

Gross total or subtotal resection of nonmetastatic medulloblastoma is associated with a better outcome than biopsy alone followed by radiation [17,18]. In two series of 113 patients, for example, the five-year actuarial survival was higher in patients with complete or subtotal gross resection compared to biopsy alone (69% versus 40%, and 78% versus 43%, respectively). Posterior fossa local control rates were also

higher with complete or subtotal resection (83% and 89% versus 27% with biopsy alone) [19, 20].

Our study showed that total resection was better than the subtotal. The median PFS and OAS for those with subtotal resection was 47 months (mean  $53.8 \pm 33$ ) in comparison to 77.5 months (mean  $76 \pm 40$ ) for those who underwent total resection, however this difference was not statistically significant ( $p=0.1$ ), which may be most probably due to small number of patients in each group. Neither the group of total resection nor that of subtotal resection could be compared to those who had biopsy because of the extremely small number of patients underwent biopsy.

The goal of surgery should be to remove as much of the tumor as possible without inflicting incapacitating neurological sequelae such as persistent ataxia or cranial nerve deficits. The importance of this limitation was illustrated by a series of 47 children in which total or radical resection could be performed in 13 patients only [21].

Several randomized studies have evaluated the contribution of adding chemotherapy to the classic treatment of medulloblastoma whether pre or post radiotherapy. Taylor et al. (SIOP PNET-3 protocol) randomized 217 patients, between 1992 and 2000, for radiotherapy alone or radiotherapy preceded by chemotherapy with vincristine, etoposide, carboplatin, and cyclophosphamide. Radiotherapy consisted of craniospinal RT, 35 Gy in 21 fractions, followed by a posterior fossa (PF) boost of 20 Gy in 12 fractions. Multivariate analysis identified the use of chemotherapy ( $p=0.0248$ ) and RT duration ( $p=0.0100$ ) as predictive of better EFS. [22].

In our study using concurrent and maintenance chemotherapy resulted in better outcome for both OAS and PFS than using radiotherapy alone (5-year progression free survival for the chemotherapy group was 70% while that of no chemotherapy group was 59% with a statistically significant difference ( $p$ -value of 0.025) and also borderline statistical difference in the estimated 5-year OAS with a  $p$  value of 0.08.

The optimal sequencing of chemotherapy and radiotherapy remains an open question.

Two randomized studies, CCG 921 [16] and German HIT-91 [23] have shown an advantage for immediate radiotherapy followed by adjuvant chemotherapy compared with pre-radiotherapy chemotherapy. The German Society of Pediatric Hematology and Oncology randomized 137 patients with medulloblastoma to receive postoperative chemotherapy (two cycles of ifosfamide, etoposide, methotrexate, cisplatin and cytarabine) prior to radiation therapy, or immediate postoperative radiotherapy with concomitant vincristine, followed by eight cycles of maintenance chemotherapy (cisplatin, CCNU, and vincristine). The pre-radiation chemotherapy group had significant myelotoxicity, which led to a higher rate of radiation treatment interruptions and an extended treatment time as compared to the maintenance chemotherapy group. The Kaplan-Meier estimates for relapse-free survival at three years were significantly higher with maintenance chemotherapy for "low risk" patients without M2/3 disease (78% versus 65%) and for patients between six and 18 years of age (84% versus 62%). In contrast, outcomes were similar for patients between three and six years old, and for those with advanced M2/3 disease, who experienced poor survival with both treatments.

One of the major concerns regarding pre-radiotherapy chemotherapy has been the potential detriment from the delay in beginning RT. In the SIOP II study [7], it was suggested that the poor outcome for the group of patients treated by chemotherapy followed by "reduced-dose" radiotherapy was probably due to the delay of radiotherapy in association with "ineffective" chemotherapy. However, the results of the SIOP PNET-3 study [22] showed that if pre-RT chemotherapy is sufficiently intensive and uses active drugs, outcome could be improved. In current studies, protocols such as the future SIOP PNET-4 protocol suggest that radiotherapy should ideally start within 4 weeks of surgery and definitely not later than 6 weeks after surgery.

By using chemotherapy, one of the main aims of current standard risk protocols is to reduce the CSRT dose and, it is hoped, reduce the long-term neuropsychological sequelae from CSRT. There is evidence that this can be achieved by post-radiotherapy adjuvant chemo-

therapy, as reported in the CCG-9892 study [24]. In that study, reduced-dose CSRT 23.4 Gy was followed by eight cycles of chemotherapy with cisplatin, lomustine, and vincristine. The progression-free survival rate at 3 and 5 years was 86% and 79%, respectively. In our study all the patients received full dose CSRT with a more or less comparable estimated 5-year progression-free survival (70% in our study vs 79% in CCG-9892 study). Reduced-dose CSRT (23.4 Gy) has formed the basis of the recently completed Children's Oncology Group A9961 standard risk study. Many studies reached this conclusion like Children's Cancer Group, and International Society of Paediatric Oncology [7,9, 24-26].

In all these studies, including the present study, the entire posterior fossa was the final target for the boost using a total dose of 54-55.8 Gy. When more conformal boost was used to include the tumor bed more or less the same results were obtained as in Merchant et al. and Douglas et al. [26,27]. The latter treated thirty-three patients with average-risk medulloblastoma with weekly vincristine concurrent with CSRT at a dose of 1.5 mg/m<sup>2</sup>. Once CSRT was completed, patients were treated with vincristine 1.5 mg/m<sup>2</sup>, lomustine, and cisplatin (75 mg/m<sup>2</sup>) for eight cycles (23 patients) or vincristine (1.5 mg/m<sup>2</sup>) cisplatin (75 mg/m<sup>2</sup>), and cyclophosphamide (1000 mg/m<sup>2</sup> according to the Children's Cancer Group protocol A9961; 10 patients). The total CSRT dose delivered was 2340 cGy. The dose prescribed to the primary tumor boost isocenter was 3240 cGy, for a total dose of 5580 cGy. The estimated 5-year disease-free survival rate was 86% with an estimated 5-year overall survival rate of 87%.

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