Medulloblastoma: review of survival at King Khalid University Hospital

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Abstract Objectives: To provide information regarding the rate of survival and the prognostic factors affecting the outcome of medulloblastoma patients in Saudi Arabia.

Materials and Methods: Retrospective review of 32 consecutive medulloblastoma patients treated at King Khalid University Hospital between 1984-1994. The tumor excision was total in 66% of patients and subtotal in 34%. Ninety-one percent of patients received radiotherapy and 19% received chemotherapy. Forty-four percent of cases had a preoperative CSF shunt while 16% required a shunt after the tumor excision. Of the 18 patients who were retrospectively staged fully using the Chang T-M system, 5 (28%) had evidence of dissemination at presentation. The death of 10 patients occurred from 1-84 (mean 23) months after presentation. Follow-up of the survivors ranged from 6-120 (mean 26) months.

Results: The overall 5 year survival rate was 53%. Seven patients had recurrent disease. Only 2 of these patients are alive at 12 and 48 months follow-up. There was no significant association between the 5 year survival rate and age, sex, evidence of desmoplasia and extent of tumor excision. A significantly better outcome was encountered in patients who had no evidence of dissemination at presentation and those who did not have a CSF shunt. The latter may be related to the fact that more shunted patients had disseminated disease at presentation.

Conclusion: The outcome of medulloblastoma patients in Saudi Arabia is comparable to what is reported from advanced centers in the West.

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KEYWORDS: *Childhood brain tumors, medulloblastoma, radiotherapy, prognosis, Collin's rule, ventriculoperitoneal shunt.*

Medulloblastoma is a common malignant tumor of the posterior fossa in children. Most medulloblastoma series published between 1983-1992 indicate that with the use of multimodality treatment protocols combining surgery, radiotherapy and chemotherapy a 5 year survival rate is to be expected in 47-63% of the affected patients.[1-5]

Medulloblastoma accounts for 20-23% of childhood brain tumors in Riyadh.[9,10] Up-to-date, information about the outcome of treatment and the rates of survival of the medulloblastoma patients in Saudi Arabia are still lacking. In 1985, Al Mefty *et al*[6] published a review of the medulloblastoma patients treated at King Faisal Specialist Hospital. The outcome and the survival patterns of the patients were, however, not determined. In this study, the authors review their experience with the treatment of 32 consecutive medulloblastoma patients treated at King Khalid University Hospital (KKUH) over a 10 year period. The aim of the article is to provide data regarding the rate of survival and the prognostic factors affecting the outcome of medulloblastoma patients in Saudi Arabia. It is accepted that the number of patients in our series may appear small, however, it must be remembered that most of the medulloblastoma series published in the international literature over the last 8 years ranged from 20-77 patients.[2,4,6,7,8,11,12]

Material and methods The medical records of 32 consecutive patients with a histologically proven medulloblastoma treated at KKUH between 1984-1994 were reviewed. There were 22 males and 10 female patients with an age range of 0.5-55 (median 10.5) years. Seventy-two percent of the patients were aged less than 18 years. The duration of history was 1-24 (median 6) weeks. The presenting clinical symptoms and signs in our

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patients were: headache in 30 (94%), vomiting in 30 (94%), disturbed level of consciousness in 10 (31%), papilledema in 23 (72%), cerebellar signs in 22 (69%), pyramidal signs in 6 (19%) and cranial nerve palsies in 6 (19%).

The histopathology reports were reviewed to identify cases with evidence of desmoplasia and glial differentiation. In the overall group of tumors, 25 (78%) were classic medulloblastomas and 7 (22%) were desmoplastic. Only one (3%) desmoplastic tumor showed evidence of astrocytic differentiation. The tumor was in the midline in 26 (81%) patients and was lateral in 6 (19%) patients. The latter were 3 adults and 3 children.

Attempts were made at staging the tumors retrospectively on the basis of their size and extent in the operative notes and CT scan studies. The Chang staging system[13] was used. The staging work-up included CT scan in all patients and cerebrospinal fluid (CSF) cytology in 18 (56%) patients. Myelography, which was not performed routinely for our patients, was negative in all 3 patients who had this investigation. The Chang T-M staging system used was as follows: T1, <3 cm limited to midline vermis; T2, >3 cm with invasion of part of 4th ventricle; T3, filling 4th ventricle, aqueduct or foramina of 4th ventricle; T4, spread to 3rd ventricle, midbrain or cervical cord; M0, no metastasis; M1, microspic tumor cell in CSF; M2, seeding of cisterns or ventricle; M3, nodular seeding of the spinal theca; M4, extra-neuraxial metastasis and MX unknown.

The surgical procedure consisted of total macroscopic excision in 21 (66%) patients and subtotal excision in 11 (34%) patients. Nineteen (59%) patients had a ventriculoperitoneal (VP) shunt for hydrocephalus. The shunt was performed prior to the tumor excision in 14 (44%) patients and after the tumor excision in 5 (16%) patients. Post operative deterioration in the neurological condition was observed in 2 patients who had invasive tumors and who were in a poor condition at presentation. One of these patients died after 1 month and the other was lost to follow-up at 6 months. Another patient, who was comatosed at presentation and who failed to improve following the tumor excision, developed a posterior fossa extradural hematoma which was evacuated. This patient also died a amonth later.

Radiation treatment was given to the posterior fossa, spine and whole brain of 29 (91%) patients. The radiation dose ranged from 4000-5000 cGy for the posterior fossa, 3000-4000 cGy for the spine and 2000-3500 cGy for the whole brain. Three patients were not given radiotherapy because of their poor clinical condition at presentation and failure to improve following surgery. All 3 patients died within 2 months after diagnosis. Chemotherapy which was not prescribed routinely, was given to 6 (19%) patients either with proven metastasis at presentation (2 patients) or after a recurrence (4 patients). The chemotherapy combination regimes consisted of BCNU, cyclophosphamide, vincristine, procarbazine and prednisolone. There were 6 other patients (19%) with either metastatic disease at presentation (3 patients) or with recurrence (3 patients) who did not receive chemotherapy because of their poor clinical condition. Survival was calculated from the date of first arrival at KKUH to the date of death or last date of follow-up. The deaths of 10 patients occurred from 1-84 (mean 23) months after presentation while the follow up of the patients ranged from 6-120 (mean 25) months. Survival was estimated using the Kaplan-Meier method.[14] These allow for the correct processing of the data of patients who are still alive and those who are lost to follow up but were alive at a certain known date. The Chi-squared test was used to compare the distribution of the variables between the following two patients groups: age: children and adults, sex: males and females, histology: classic and desmoplastic, extent of excision: total and subtotal, CSF shunting: performed and not performed, Chang tumor staging: T2 and T3, 4 and M0 and M1-3.

Results The overall survival rate is shown in Fig. 1. The Chang T-M distribution of our patients at presentation was as follows: T1, 0; T2, 22 patients (69%); T3, 9 patients (28%); T4, 1 patient (3%); M0, 13 patients (41%); M1, 3 patients (9%); M2, 2 patients (6%); M3, 0 and MX, 14 patients (44%). The data of patients with recurrent and metastatic disease are summarized in Table 1, while Table 2 summarizes the correlation of the various prognostic factors with the survival rate. The better outcome in the patients who were not shunted compared to those who had a shunt may be related to the fact that the 5 patients that had disseminated disease at presentation and the 3 patients that did not have radiotherapy all had a shunt.

Only 2 patients survived beyond the risk period defined by Collin's rule[15] which states that the period for recurrence is equal to the age at presentation, plus 9 months of gestational age. One of these patients, who was aged 4 years at presentation, developed a recurrence after 6 years and is still alive 4 years later, while the other

patient, who was aged 10 months at presentation, has survived 6 years without recurrence.

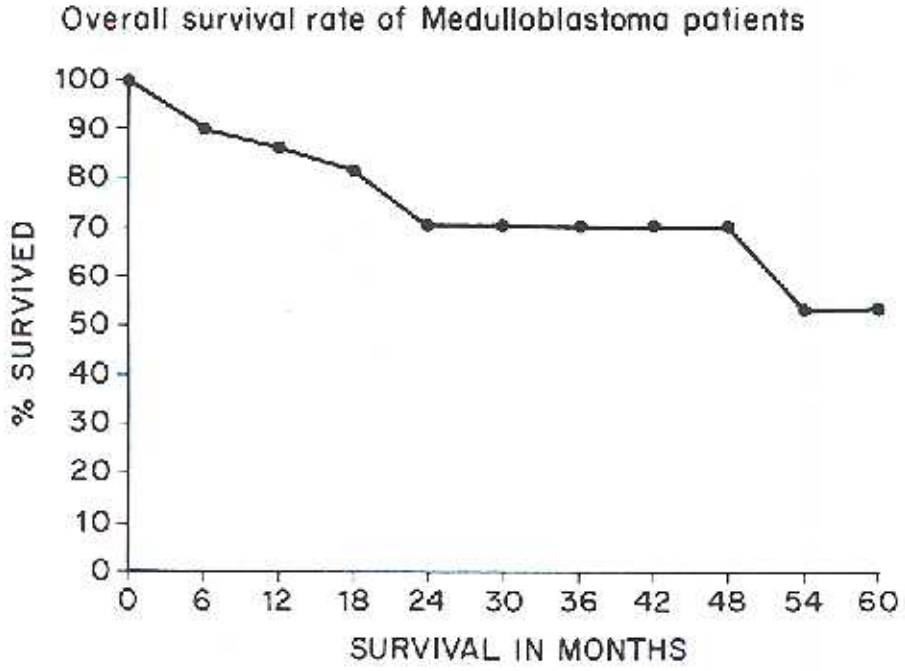
Discussion Based on our experience, the incidence of medulloblastoma in Riyadh is 4 cases/1 million population/year[9] which is comparable to the incidence reported from the West.[16] The peak frequency of this tumor in children (median age of our patients 10.5 years) is in keeping with other reports.[1,4,11,16] We did not find a significant difference in the survival rates between children and adults which is in agreement with a few other reports,[2,4,8] but not others.[8] Most authors suggest that children more than 6 years of age do better than those aged less than 6 years, since younger children are more likely to have dissemination of the disease at presentation and to have less aggressive treatment.[1,3,5,6,17,18]

The male dominance in our series (2.2:1) is a confirmation of previous reports.[1,4,5,11,16] We found that sex had no significant difference on the overall survival rate which is in agreement with some reports,[1,2,4] but not others, who found improved survival rates in females.[8,16] The signs and symptoms of raised intracranial pressure and cerebellar dysfunction were the commonest initial features and the relatively short history is typical.[1,4,5,11,16,17] Thirteen percent of the children and 33% of the adults in our series had a laterally located tumor which is usually associated with a more favorable outcome.[5,8,16] Maleci *et al*[8] reviewed the literature and found that out of a total of 1635 reported cases, 11% of pediatric tumors and 43% of adult tumors were located laterally.

The effect of the histologic type and cellular differentiation is a controversial issue.[4] Desmoplasia, which is seen more frequently in adult tumors,[1,19] has been associated with a better outcome in some series,[8,16,19] but not others.[1,4,8] Better survival has also been reported in association with cellular differentiation by some authors[2] but not others.[3,4] There was no significant difference in the outcome of patients with desmoplastic or classical medulloblastoma in this series.

The influence of extent of surgery on the overall outcome is controversial.[4] Some reports suggest a significant difference in the overall survival rates of patients who had total excision compared to those who had a subtotal excision,[1,7,8,12] while others, in agreement with our findings, do not find a significant difference.[2,3,4,5,17] Nevertheless, the use of the microscope is likely to result in a more complete removal of the tumor and our current practice is to attempt total excision of all the apparent tumor when possible.

Medulloblastoma is exquisitely radiosensitive and the radiation therapy remains the most significant determinant of outcome in patients with this disease. The safe effective radiation doses to the brain and spinal cord are, however, not clearly defined. Our patients received the standard radiation doses recommended in the literature. Most authors advise delivering at least 5000 cGY to the posterior fossa.[2,4,6,8,13] Caputy *et al*[2], however, found no significant difference in the outcome of patients treated with a posterior fossa



dose of 4000-5000 cGY and those treated with a dose of 5000-5500 cGy. Since the survival of medulloblastoma patients is significantly better when the neuraxis is irradiated, a dose of 3000-4000 cGy to the spine and 2500 4500 cGY to the whole brain are recommended.[4,6,9] With increasing recognition of the long term adverse effect of radiotherapy, it has been suggested that patients who were carefully staged and found to have only localized disease can be treated by a smaller dose of craniospinal radiotherapy (2500 cGY).[3,6,12]

The importance of careful postoperative staging by myelography (or more recently MRI with gadolinium) and cerebrospinal fluid (CSF) cytology was emphasized by Deutsh *et al*[18] who found that at presentation 45% of patients had evidence of dissemination beyond the posterior fossa, and that spinal cord lesions were demonstrated in 26%. Tomita and McLone[13] found positive myelographic findings in only 8.3% of their cases and suggested that the previously reported 36-43% positive results in the literature may have been exaggerated by blood or segmental arachnoiditis, hence, it is recommended that myelography be performed 2-3 weeks after surgery. Only 56% of our patients had cytologic assessments and we found evidence of dissemination at presentation in 28% of these patients. The latter proved to be a poor prognostic factor. In the literature, there are authors who failed to detect a correlation between Chang T-M staging and prognosis[2,4,12] and others who found that patients with T1-2, MO tumors did better than patients with T3-4, M1-3 tumors.[3,8,17,18]

In this series, we are aware of 7 patients that had recurrent disease which involved neuraxis in 5 (71%) of these patients and was extra-neuraxial in 3 (43%) of these patients (Table 1). The locations of the neuraxial recurrences were: cerebellum 2 (40%) patients, supratentorial area 3 (60%) patients and CSF 1 (20%) patient. Garton *et al*[4] reported that the posterior fossa is the commonest location of recurrence (79%) while the supratentorial area involved is 47% and the spine 59%, and that recurrence is extra-neuraxial in 21% of patients. Only 2 of our 7 patients with recurrent disease were alive at follow-up of 12 and 48 months respectively.

Chemotherapy as an adjuvant modality in the treatment of medulloblastomas remains investigational. Multi-institutional, randomized trials using combined agents have demonstrated a slightly improved disease free survival time for poor risk patients receiving chemotherapy.[3,6,20] Chemotherapy may be useful in delaying disease recurrence but does not significantly prevent recurrence[3,6,20] Various agents have shown efficacy in patients with recurrent medulloblastoma. In the majority of patients the efficacy is only transient, nevertheless, a 2 year survival in 46% of cases with recurrences has been reported.[4] Chemotherapy is most useful in young children (aged less than 2 years) in whom there

Table 1: Patients with recurrent and metastatic medulloblastoma.

Time to Recurrence (Months)	Site of Recurrence	CSF Shunt	Recurrence Treatment	Outcome	Survival after Recurrence (Months)
10	Scrotal mass	+	Excision	Deteriorated & died	1
18	Spinal CSF	+	———	Deteriorated & died	1
28	Pelvic mass	+	DXT & Chemotherapy	Unchanged (lost to follow-up)	4
48	Supratentorial Subarachnoid	+	———	Deteriorated & died	1
48	Cerebellum, Suprasellar, pelvic mass	—	DXT and chemotherapy	Improved	12
72	Frontal lobe	—	Excision and chemotherapy	Improved	48
84	Cerebellum	—	Excision and chemotherapy	Deteriorated & died	7

Table 2: Correlation of prognostic factors and survival rates of 32 patients with Medulloblastoma.

Factors		No. of Patients	Survival Rate			Significance
			1 Year	3 Years	5 Years	
Age:	Children	23	71%	51%	51%	
	Adults	9	100%	100%	60%	NS
Sex:	Male	22	85%	62%	62%	
	Female	10	89%	89%	29%	NS
Histology:	Classical	25	82%	64%	53%	
	Desmoplasia	7	100%	100%	50%	NS
Excision:	Total	21	90%	81%	54%	
	Subtotal	11	78%	48%	48%	NS
Shunting:	Performed	19	76%	46%	15%	
	Not performed	13	100%	100%	100%	P=0.025
Chang T Stage:	T2	22	95%	82%	62%	
	T3,4	10	78%	42%	42%	NS
Chang M Stage:	M0	13	100%	100%	84%	
	M1 3	5	40%	20%	20%	P=0.01

was extensive tumor invasion and incomplete excision to delay the need for radical radiotherapy.[7] Only 19% of our patients received chemotherapy. It is appreciated that most centers in the West nowadays treat their medulloblastoma patients following surgery by a protocol combining radiotherapy and chemotherapy. The lack of radiotherapy facilities in our hospital makes the application of such protocol more difficult.

Forty-four percent of our patients had a VP shunt prior to tumor excision. Most of these were done early in the series when it was our routine to perform a shunt as a first stage for all patients with significant hydrocephalus. In recent years direct tumor excision with temporary external ventricular drainage has been adopted. Preoperative shunts have been implicated as a route for systemic spread of intracranial tumor. Three of our patients had extra-neuraxial spread (Table 1) and in only one of these patients the shunt was responsbile.[21] In the other shunted patient the pelvic mass was due to a direct spread of the tumor.[22] In a critical review of the literature, Jamjoom *et al*[21] found that out of 160 cases with systemic metastasis 18.7% had a shunt and that the shunt was the route of spread in no more than 6.9%. In most of these patients the outcome was determine by the concomitant intra-axial recurrence suggesting that the chance of medulloblastoma metastasizing through a shunt and adversely affecting the outcome is very small indeed. In this series, there was a significantly better survival rate in patients who did not have a shunt. This is mainly because shunted patients had a higher incidence of disseminated disease at presentation and 3 of the shunted patients were in very poor condition at presentation and died early.

Our 5 year survival rate of 53% is within the range of that reported in the literature in recent years.[1-8] The recurrence in one of our patients occurred beyond the Collin's period, suggesting a failure rate of 14% in applying Collin's rule for the cases that had a recurrence in our series. It has been reported that in 0-43% of patients the recurrences occur beyond the period of risk.[1,2,6] Belza *et al*[6] suggested that patients who survive a critical early period of 8 years have a high likelihood of remaining disease-free.

There is increasing recognition that the success in the treatment of medulloblastoma exacts a price from these patients in terms of a compromised quality of life. As a result of radiotherapy treatment (and to a lower extent chemotherapy treatment), the long-term medulloblastoma survivors tend to demonstrate a substantial growth retardation, neurological, behavioral, and neuro-psychological sequelae.[1,3,17,23] The follow-up of our patients is relatively short for us to comment on the quality of their long term survival. We, however, observed that the few number of children still alive more than 5 years after diagnosis are small for their age and are having educational difficulties.

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ورم الخلايا الأرومية النخاعية: مراجعة للبقاء في مستشفى الملك خالد الجامعي

الهدف: إعطاء معلومات عن معدل البقاء والعوامل التي تؤثر على نتيجة علاج ورم الخلايا الأرومية النخاعية الشوكية في المملكة.

الطريقة: تم إجراء دراسة استرجاعية شملت ٣٢ حالة ورم للخلايا الأرومية النخاعية التي تم علاجها بمستشفى الملك خالد الجامعي بين ١٩٨٤ - ١٩٩٤م. كان استئصال الورم كاملاً في ٦٦ في المائة وتحت الكامل في ٣٤ في المائة. تم علاج ٩١ في المائة من المرضى بالعلاج الشعاعي و١٩ في المائة بالعلاج الكيماوي. أجرى إلى ٤٤ في المائة عملية لتصريف السائل الدماغي النخاعي قبل استئصال الورم، وأجريت إلى ١٦ في المائة مثل هذه العملية بعد استئصال الورم. من الثمانية عشر مريضاً الذين تم بالاسترجاع تحديد مرحلة أورامهم بنظام تشانج ٥ (٢٨ بالمائة) كان عندهم أدلة على انتشار الورم وقت التشخيص الأول. متابعة البقايا كانت من ٦ - ١٢٠ (المتوسط ٢٥) شهراً.

النتائج: كان معدل البقاء العام بعد ٥ سنوات ٥٣ بالمائة. سبعة من المرضى عانوا من رجوع الورم، اثنين من هؤلاء المرضى لا يزالوا على قيد الحياة ١٢ و٤٨ شهرا بعد المتابعة. لم تكن هناك علاقة مهمة بين معدل البقاء بعد ٥ سنوات والعمر، الجنس ووجود مظاهر التنسج الليفي ومدى الاستئصال، ولكن وجد بقاء أفضل للمرضى الذين لم يكن ورمهم منتشراً عند التشخيص.

الاستنتاج: نتيجة علاج ورم الخلايا الأرومية النخاعية في المملكة هي مماثلة لما نشر من المراكز المتطورة في الغرب.