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Experience of 20 years in Management of Medullohlastoma (A long – term Retro spective study)

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Abstract :

Treatment for patients with newly diagnosed medulloblastoma includes surgical resection followed by craniospinal radiotherapy. Adjuvant chemotherapy has been shown to increase the cure rate with high risk or average risk disease and is now a standard part of contemporary management ***(Gajjor et al., 99).***

Advance in surgery and radiotherapy techniques have improved results in the last few decades ***(Paker 1999)***. These procedures have important early and long term morbidity that must be weighted in order to offer the patient an acceptable risk-beniefit likelihood.

The purpose of this study was to analyze the various clinical and prognostic features which might affect the survival of medulloblastoma and to asses the response of patients to treatment.

This study includes 288 patients with medulloblastoma who were treated in both Neurosurgical and Radiation Oncology Departments during the period 1981 and 2000.

Statistical analysis has proven that the median survival was not affected significantly by the sex or site of tumor but the most significant variables that affected the median survival were the extent of surgery and stage of the tumor, age and histopathology. Shunt operation reduces the incidence of post operative mortality markedly.

Introduction:

Medulloblastoma constitutes from 10% to 20% of primary CNS tumors in children and about 40% of all posterior fossa tumors *(Heideman et al., 1997)*.

Surgical removal of the tumor is considered the first step of treatment to establish definite diagnosis, releive the acute symptoms and reduces the bulk of tumor *(Brandes et al., 1999)*. Total or near total resection exerts an important infleunce on recurrence of medullob - lastoma *(Bailey et al., 1995)*.

The prognosis for medullob -lastoma has improved remarkably in the past 40 years as a consequence of advances in radiotherapy *(Brandes et al., 1999).*

In *1994, Carr et al.,* reported a trend of better survival in adult patients treated with chemotherapy meanwhile adjuvant chemotherapy was of value if given for patients with high risk of recurrence *(Brandes et al., 1999).*

Recently *Millot et al., 1999*, reported encouraging results with the

use of high dose chemotherapy with stem cell support after surgical resection and craniospinal irradiation for newly diagnosed medulloblastoma patients in high risk group.

Patients & methods

The medical records of patients with medulloblastoma treated in both Neurosurgery and Radiation Oncology Departments, Ain Shams University during the period 1981 and 2000 Medical records were studied those with incomplete data or lost follow up before ending prescribed treatment were excluded.

The studied patients were classified into two groups according to their age, group I, included 200 patients below or equal to 16 years, and group II, included 88 patients above 16 years of age.

The following criteria were studied:

1. Personal and medical history,
2. General and neurological examenation.
3. Performance status according to karnofosky scales
4. Radiological studies with either CT scan or MRI or both.
5. Histopathological examination & CSF cytology
6. Staging according to Chang staging system.
7. Details of different treatment modalities.
8. Toxicity and morbidity of treatment according to WHO system.
9. Survival was calculated from first day of treatment to the last fullow up

All the studied different parameters were analyzed statistically to find out the most important prognostic factors affecting the median survival. Three year cumulative survival was estimated and analyzed versus the various prognostic factors including age at diagnosis, sex, duration of symptoms and sings, CSF cytology hisotpath - ological results, site, stage of tumor, extent of surgical intervention and post operative therapy.

Results

For a convenient statistical approach and conclusive analysis of the obtained results, it was crucial to separate the studied patients into 2 groups below or equal and above 16 years. The mean survival for all cases was 26.4 + 15.9 months.

The range of age for the studied patients was 3-29 years, the majority of patients were in pedeatric group (200 patients)

Male to female ratio was 1.4 : 1.

The duration of symptoms prior to diagnosis ranged between 1 to 6 months, with a mean value of 3.5 + 1.7 months.

The main presenting symptoms were those of increased intracranial tension (headache, vomiting and blurring of vision) in 80% patients followed by incordination 72% and cranial nerves offection 55%.

CSF cytology was doun in 182 patients only and it was positive in 26%. (47/182).

Histopathology analysis or 130 cases, desmoplastic variant was described in 28.5% of them meanwhile the remain - ing was classic form.

The site of tumor was midcerebellar in 57% but lateral cerebellar tumor was found in 43%.

T. Staging was done according to chang et al., 1969 staging system, T3 and T4 cases were significntly higher in both age groups (66%). Radiological findings by C.T. revealed that the highest majority of patients had a large tumor associated with obstructive

hydrocephalus ranging between mode - rate (32%) and severe degress (68%). Perifocal edema was evident in 70% the tumor was hyper dense in 81% of patients.

- Treatment modelities done (surg -ery, radiotherapy and chemother - apy).
- Surgery includes biopsy, partial resection and total resection with or without shunt operation
- Toxicity and morbidity of treatment

1. Surgery: was the first line of treatment for all cases in the form of either total excision or subtotal excision. Gross total excision was performed for 82 patients (28%) in whom were shunted preoperatively (64 patients). Subtotal excision was performed for 186 patients (64.5%) The shunt was done for 43 of them. Meanwhile shunt operation was done with no tumor surgery for 20 patients only (7%) of all patients
2. Radiation therapy: Craniospinal radation therapy was performed for all cases, with either Co 60 or linear accelerator 4 Mv Craniospinal radiation was given for all cases using either Co60 or linear accelerator 4Mv. With dose ranging 3600 to 5400 cGy to the posterior fossa and from 2000 to 3000 cGy according to the age of patients.
3. Chemotherapy was given for recurrent cases only (50 cases) in the form of CCNU vincristine and Natulan. unfortunally most of cases died after 2 or 3 courses.

Recurrence or progression of tumor were recorded in 68% of the cases. Extra – CNS metastasis included long bones, lymph nodes and liver occurred in 18 cases (10%) The can-mmonest site of recurrence was at the primary tumor site 972%) followed by spinal metartases (18%).

Median Survival analysis:

Older age group showed significant higher median survival compared to younger age group (P <.05). but patients younger than 4 years old had poor median survival.

Sex did not significantly affect survival the symptoms prior to diagn - osis ranged between 1 to 6 months, with a mean value of 3.5 + 1.7 months. so that most of cases were T_3 & T_4.

Desmoplastic type was evident in 15% of younger age group and 55.8% in older one with significantly higher medi -an survival for desmoplastic type in comparison to classic varian type ($P < 0.05$)

The commonest site of medulloblastoma in group I was the cerebellar vermis (62%) meanwhile the commonest site for group II was the lateral cerebellar region 53% with median surveval 35.01 and 36 respectively which was not significant.

The median survival for T_1 & T_2 patient was significantly higher than those with T_3 & T_4 palients Pvalue was highly significant ($P < 0.01$).

The cummulative survival calcul - ated for patients with statistical compa - rison for the extent of surgery in each group showed a high significant in the survival of the shunted patient ($P = < 0.01$) due to decrease in post operative mortality and morbidity of treatment. On the other hand, statistical

Comparison calculated for 207 patients who were all shunted, showed a highly significant increase infavor of total excision versus biopsy or subtotal excision ($P < 0.01$).

Discussion

The current study demonstrates that medulloblastoma patients constitute 10% of all primary malignant tumors referred to Radiation Oncology

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In a study NEMROCK, Egypt, between 1981, 1998 the incidence was 8.4% *(Helmy et al., 2000)* which was similar to that reported by Hadad et al., in 1986 (8.5%). However lower incidence was reported by *Poldnak and Flammery in 1995.*

The age of studied patients ranged between 3 to 29 years with a mean age of 11.3 years. 70% of the cases were below 16 years similar to that reported by ***Sheikh and Kanaam, 1997 . and Hadad et al.,*** *1986* which was 10.1 years and Walpren and Friedman 1996, which was 11.3 years.

In this work, medulloblastoma constitute 23% of all primary brain tumor in pediatric age group which is nearly similar to that reported *Weidman et al. 1997* which was 20%.

According to Chang staging system, 34% of the analyzed cases were classified as T_1 and T_2 and 66% of them were T_3 and T_4 stages. However Zelter et al., 1999, reported that 59% of 188 cases were T_1 and T_2 while 41% were T_3, T_4. The higher percentage of advanced cases in Egypt may be explained by the delayed presentation to physician.

Analysis of histopathological repo - rts showed a significantly median survival for desmoplastic type. On the other hand, Aragones et al., 1994, reported 5-year survival in desmoplastic variant compared to the classic type.

Histopathological study revealed that the desmoplastic type represented 15% of patients of younger age group but it was 55.8% in the older group in comparison to the classic type.

Histopathological variant in our study had significant higher median survival in favor to desmoplastic type ($P < 0.05$). Nevertheless, both *Sheikh and Kanan, 1994, and Ildan et al., 1994,* considered desmoplastic type a favor -able prognostic factor.

Disease free survival for the high risk group of patients was 20% meanwhile for the low risk group was 50%.

Diagnosis of medulloblastoma was mainly carried by computerized axial tomogrophy in the first 10 years of the study *(Moawuad, et al., 1987).*

As regard surgical intervention, patients were devided in to two main groups either shunted or non shunted group which were subdevided into subgroups according to the extent of surgery.

Statistical comparison of the median cumulative survival between shunted and non shunted patients in both surgical groups (total subtotal/ biopsy groups) revealed a highly significant prolongation in the median survival $P < 0.01$ in patients who underwent shunt operation. This has been shown by *Salama et al., 1986* as well as Moawad et al., in 1987. Stating that CSF shunt had reduced dramatically post operative mortality from 46% to 11% and improved the survival of patients. Which was in contrast to that reported; *Bloom and Bessel, 1989,* preoperative shunt was advised to be avoided as a source of dissemination. In this report they suggested that shunt operation might be a chance for tumor dissemination and better to be avoided

From the analysis of previous results, it could be concluded that total excision with pre-operative shunting is the optimum modality as compared with minimal excision of the tumor. This findings agree with those reported by *Boyett et al., 1995, and Baily et al., 1995.*

Recently, *Zeleter et al., 1999* had also encourged aggressive resection of the tumor of the tumor in their study of 188 patients.

The median survival of patients with medulloblastoma has been reported to have increased significantly in the last decade which is mainly due to improvement of techniques including the entire cranial spinal axis irradiation and increasing the dose to the reurocranium and to the posterior possa., as well as improvement of diagnostic technique (CT & MR1). Together with the new trend of more radiacl resection aided by advances in microneurosurgery as well as improvement in the techniques of post operative radiation using computer planing system with simulation and the use of linear accelerator with multiple energies *(Brandes et al., 1999).*

Inspite of improvement in the survival of the patients with medulloblastoma as a response to radiotherapy a wide range of short and long term side effects are reported *Branches et al., 1999*. Bone growth reladation, behavioral and inletlectual dysfunction and pituitary hypo thalamic dysfunction have been widely reported.

It could be concluded that the optimum surgery together with the adjuvant radiation therapy, are the main reasons behind prolongation and better quality of the long-term survival of patients with medulloblastoma.

Table (1) Clinical and pathological findings of 288 patients with medulblastoma

Age		
Below 16 ys	200	(69.4%)
Above 16 ys	88	(30.6%)
Mean age	[11.3 yrs (136 + 90.58 months)	
Sex		
M	160	(55.6%)
F	128	(44.4%)
Symptoms of ↑ ICT.	230	(80%)
Incoordination	207	(72%)
Cranial N. Palsy	158	(55%)
CSF Cytology	(182)	
+ ve	47	(25%)
- ve	135	(75%)
Histopathology analysis	(130)	
Desmoplastic	37	(29%)
Non Desmoplastic	93	(71%)
Site of tumor		
Mid Cerebellar	165	(57%)
Lat Cenchbellar	123	(43%)
Stage		
T_1, T_2	99	(34%)
T_3, T_4	189	(66%)

Table (2) Surgical Treatment Modalities of 288 cases with Medulloblastoma.

a) Shunted group:	(209)	
Total excision	(64)	(31%)
Subtotal excision, biopsy	(125)	(60%)
Shunt only	(20)	(9%)
b) Non Shunted group	(79)	
Total excision	(18)	(22%)
Subtotal excision, biopsy	(61)	(78%)

Table (3) Radiological findings in 288 cases with medulloblastoma

Finding	Number	%
Hydrocephalic changes		
moderate	92	32%
severe	196	68%
Perifocal edema	202	70%
Density be fore contrast		
Hyperdense	233	81%
Isodense	20	7%
Hypodense	35	12%
Enhancement after contrast.		
Positive	228	79%
Negative	60	21%
Cystic areas and heterogenicity	32	11%
Calcification	17	6%

Table (4): Correlation of important prognostic factors versus 3-year survival for 153 patients with medulloblastoma

	No	Cummulative survival at 36M.	Median survival	P.Value
Age				
< 16 years	108	0.0535	31.51	Sig.
> 16 years	45	0.1967	36+	<0.05
Sex.				
Male	83	0.1117	36+	Non
Female	70	0.0762	36+	Sig.
Histopathology				
Desmoplastic	12	0.2857	36+	Sig.
Non-Desmoplastic	60	0.0375	31.41	<0.05
Site of tumor				
Cerebellar vermis	94	0.1016	35.01	N.S.
Lateral cerehellar	59	0.0813	36+	
Staging				
T1, T2	59	0.1823	36+	H.S.
T3, T4	94	0.0237	29.45	<0.01
Surgery				
Biopsy subtotal	52	0.0423	22.16	H.S.
Total resection	60	0.1024	36+	<0.01

* The remaining patients had insufficient follow up.

Table (5) Complications of external radiations in 153 patients with Medullablastoma.

Complications	Number	%
➢ **Early complications:**		
Alopecia	153	100%
Myelosupression On top of spinal nadiation	38	22%
Otitis media	20	13%
➢ **Late complications**		
Growth Hormonal Deficiency	29	19%
Decrease in the inellectual dysfunction	31	20%

Fig I : Cummulative Survival in 288 Patients wrth medulloblastoma as regard the age

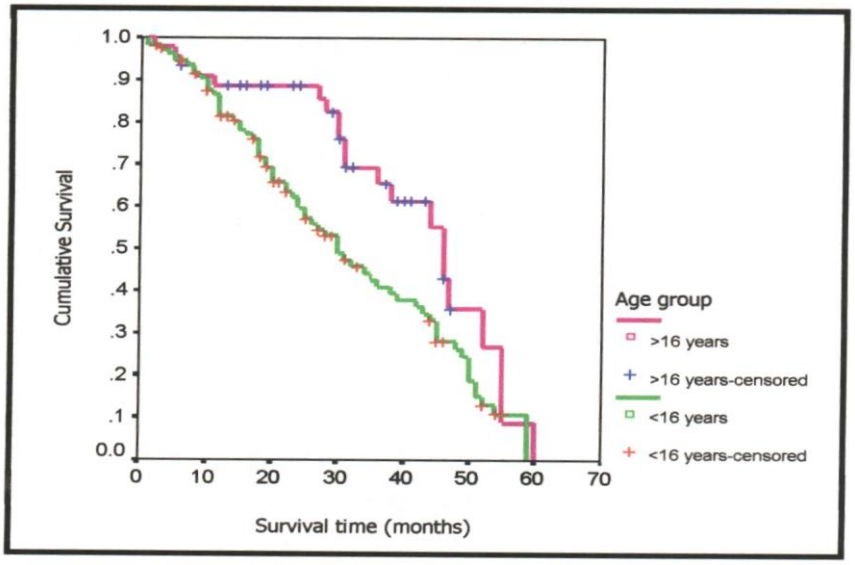
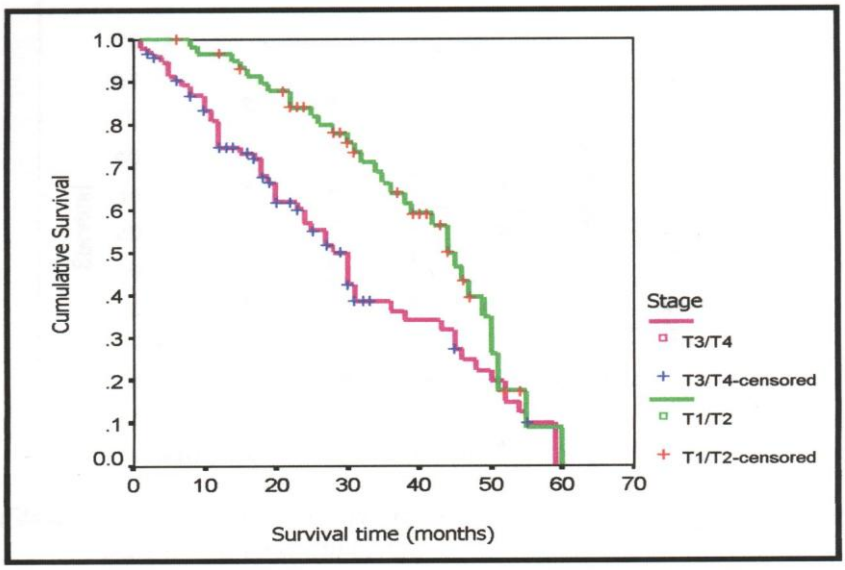
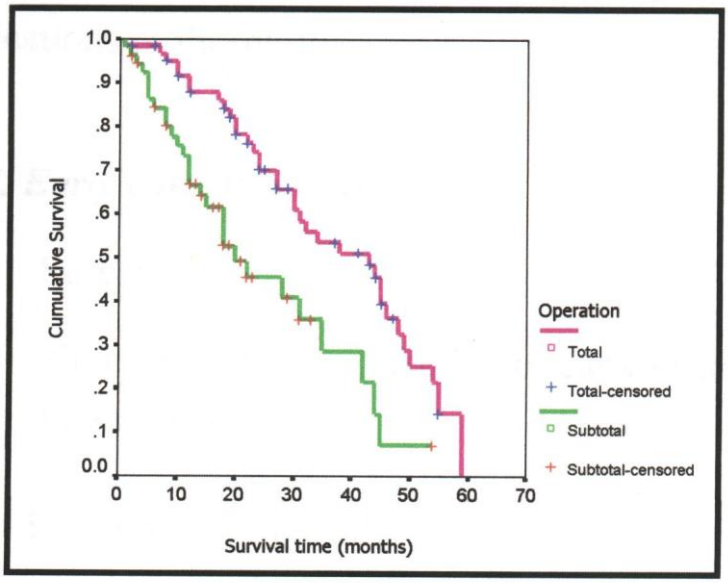


Fig II : C ummulative Survival in 288 Patients wrth medulloblastoma as regard stage



FigI : Cummulative Survival in 288 Patients wrth medulloblastoma as regard tyvse of surgesy



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دراسة لخبرة عشرون عاماً في علاج اورام (الميضاللو بلاستويا) بدائيات الدبق العصبي (داسة بأثر رجعي علي المدي البعيد)

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ملخص البحث

يشتمل علاج مرضي بدائيات الدبق العصبي بعد التشخيص الحديث علي الاستئصال الجرعي ثم العلاج الاشعاعي علي المخ والقناة العصبية

العلاج الكيميائي المكمل ثبتت فعاليته في زيادة معدل الشفاء للمرض ذو الخطورة العالية ويعتبر علاج اساسي مكمل للمرض ذو الخطورة الوسطي.

ولقد تحسنت نتائج العلاج مع تقدم اساليب الجراحة والعلاج الاشعاعي.

ونظراً لوجود آثار جانبية لهذه الاساليب العلاجية علي المدي القصير والبعيد فإن التقنية يعتبر هاماً في استخدامها للحصول علي درجة قليلة من الاثار الجانبية المصاحبة للعلاج.

كان الهدف من هذا البحث هو تحليل العوامل المنذرة المختلفة والتي قد تؤثر علي معدل استمرار الحياة وكذا استجابة المرض للعلاج.

ولقد شملت هذه الدراسة علي 288 حالة من مرضي الميضا للوبلاستوما والذين تم علاجهم في قسمي كل من جراحة المخ والاعصاب وعلاج الا ورام بالاشعاع والطب النووي في الفترة التي تمتد بين عام 1981 حتي عام 2000.

ولقد اثبت التحليل الاحصائي الي ثبوت ان متوسط استمرار الحياة لايتأثر بالجنس او مكان الورم ولكن يتأثر بشكل كبير بدرجة الاستئصال الجراحي للورم، مرحلة الورم، عمر المريض وتحليل الانسجة، بينما تعتبر عملية تحويل السائل النخاعي من العوامل المؤثرة للتقليل من الوفاة الناتجة من التدخل الجراحي بنسبة عالية.