Prognostic Factors, Complication, and Patterns of Relapse in Adult Medulloblastoma

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Objectives: This study aimed to determine the outcome of a management policy for adult medulloblastoma and to evaluate the impact of proposed prognostic factors on the outcome.

Patients and Methods: The study included 15 adult patients; 9 males and 6 females with mean age of 25.5 ± 9.3 years and had newly diagnosed; biopsy-confirmed medulloblastoma confined to the craniospinal axis. There were 11 lateral and 4 midline lesions and 12 patients had hydrocephalus. Headache, and nausea and vomiting were the commonest presenting symptoms with a mean duration of symptoms of 6.1 ± 3 weeks. All patients underwent brain MRI; brain CT scan for 5 patients and spinal evaluations was conducted. All patients underwent surgical resection followed by external-beam radiotherapy to the entire craniospinal axis and 7 patients had chemotherapy. Regular follow-up visits for clinical and radiological assessment were designed.

Results: Patients having hydrocephalus underwent ventricular shunt procedures prior to surgical resection. Total resection was feasible in 8 patients, subtotal resection in 4, and partial resection in 2 patients. One patient had only biopsy and resection was infeasible. Radiotherapy was initiated after a mean duration of 40 ± 20 days after surgery and the median duration of radiotherapy was a 60 ± 20.5 day. The mean duration of follow-up was 36 ± 18; range: 6 to 72 months. Five patients had experienced recurrences after mean duration of follow-up of 18 ± 12.5 months; 3 recurrences were in the surgical beds and 2 as bone metastasis. Three patients had recurrence died with a 3-year relapse-free of 66.7%, the 3-year morbidity secondary to recurrence was 13.3% with a 3-year mortality rate of 20%. There was a negative significant correlation between possibility of relapse and the extent of surgical resection and was found as a specific predictor for relapse-free postoperative course.

Conclusions: The assumed policy of surgical resection, as much as possible, followed by radio and chemotherapy was appropriate therapeutic modality for adult medulloblastoma with 3-year relapse-free life of 66.7%. The extent of surgical resection was found as a specific predictor for prognosis after such treatment policy.

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Medulloblastoma is the most common CNS tumor of childhood, accounting for 15% to 30% of all childhood brain tumors, and 30% to 40% of all posterior fossa tumors[1] with the peak age at presentation is 5 to 10 years.[2] Medulloblastoma is classically defined as a primitive neuroectodermal tumor arising in the cerebellum with predominant neuronal differentiation and is classified as grade IV under the World Health Organization (WHO) grading system.[3]

Although medulloblastoma most commonly affects children, 15% to 36% of cases are reported to occur in adults.[4] Despite such frequency, medulloblastoma was considered rare in adults and is diagnosed in approximately 0.5 of 100,000 patients per year.[5]

The past decades have seen an increase in the survival rates of patients with standard-risk medulloblastoma. Efforts have, therefore, been focused on obtaining better results in the treatment of patients with high-risk tumors. In addition to consolidated therapies, novel approaches such as small molecules, monoclonal antibodies, and antiangiogenic therapies that aim to improve outcomes and quality of life are now available through new breakthroughs in the molecular biology of medulloblastoma.[6] The advent of innovative anticancer drugs tested in brain tumors has important consequences for personalized therapy. Gene expression profiling of medulloblastoma can be used to identify the genes and signaling transduction pathways that are crucial for the tumorigenesis process, thereby revealing both new targets for therapy and sensitive/resistance phenotypes.[7] The interpretation of microarray data for new treatments of patients with high-risk medulloblastoma, and other poor prognosis tumors, should be developed through a consensus multidisciplinary approach involving oncologists, neurosurgeons, radiotherapists, biotechnologists, bioinformaticists, and other professionals.[8]

In the past few years, thanks to a multidisciplinary approach including surgery, chemotherapy and radiation therapy, survival has significantly improved. Despite that, a third of patients still have a low chance of being cured and long-term survivors experience severe treatment-related sequelae.[9] Medulloblastomas are usually classified

according to clinical risk stratification, based on histological features, age at diagnosis, extent of tumor resection and the presence or absence of metastases. However, these clinical variables always need to be verified for defining risk-related disease.[10]

This study aimed to determine the outcome of a management policy for adult medulloblastoma and to evaluate the impact of proposed prognostic factors on the outcome.

PATIENTS AND METHODS

This study included 15 adult (older than 16 y) patients with newly diagnosed; biopsy-confirmed medulloblastoma confined to the craniospinal axis and received their curative treatment at Cairo University hospitals throughout the period since January 2002 till January 2008. There were 9 males and 6 females with mean age of 25.5 ± 9.3; range: 17 to 47 years.

There were 11 patients with lateral lesions and 4 patients with midline lesions. Headache, and nausea and vomiting were the commonest presenting symptoms reported in 15 (100%) and 13 patients (86.7%), respectively. Truncal ataxia was reported in 12 patients (80%) and each of nystagmus and vertigo was reported in 10 patients (66.7%). There were 3 cases (20%) of cranial nerve palsies and 1 case (6.7%) of cord compression and 12 patients (80%) had moderate-to-severe hydrocephalus, (Table 1).

Duration of symptoms was significantly longer ($t = 6.691$, $P < 0.01$) in patients with lateral lesions (7.5 ± 1.9; range: 6 to 12 wk) compared with those had midline lesions (2(0.8; range: 1 to 3 wk) with a mean total duration of symptoms was 6.1 ± 3; range: 1 to 12 weeks, (Table 2).

Studied patients underwent radiologic assessments included brain MRI for all patients, (Figs. 1, 2) and brain CT scan for 5 patients. Spinal evaluations included MRI scans, and cerebrospinal fluid cytological examinations in all cases. Bone scans were done for 5 patients at the time of presentation. Each patient underwent staging according to the Chang staging system, (Table 3).[11]

TABLE 1. Patients' Characteristics and Preoperative Data

Age (y)	25.5 ± 9.3 (17-47)
Sex	
M:F	9:6
Site of lesion	
Lateral	11 (73.3%)
Midline	4 (26.7%)
Presenting clinical picture	
Headache	15 (100%)
Nausea and vomiting	13 (86.7%)
Truncal ataxia	12 (80%)
Nystagmus	10 (66.7%)
Vertigo	10 (66.7%)
Cranial nerve palsy	3 (20%)
Spinal cord compression	1 (6.7%)
Hydrocephalus	12 (80%)

TABLE 2. Duration of Symptoms in Patients Categorized According to Site of Lesion

Site of lesion	Mean ± SD	Statistical analysis
Lateral lesions	7.5 ± 1.9 (6-12)	$t = 6.691$
Midline lesions	2 ± 0.8 (1-3)	$P < 0.01$

All patients were assigned for medulloblastoma resection, the extent of resection was determined intraoperatively according to its feasibility to range between complete resection to biopsy only. Resected tumor was sent for histopathological examination. All patients received external-beam radiotherapy to the entire craniospinal axis as part of management policy. Regular follow-up visits for clinical and radiological assessment were designed.

Statistical Analysis

Obtained data were presented as mean ± SD, ranges, numbers, ratios, and percentages. Results were analyzed using paired t test. Possible relationships were investigated using Pearson linear regression. Sensitivity and specificity of analysis of patients' demographic data, preoperative findings, extent of surgical resection, duration of radiotherapy, as predictors of relapse-free postoperative course were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC). Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. P value less than 0.05 was considered statistically significant.

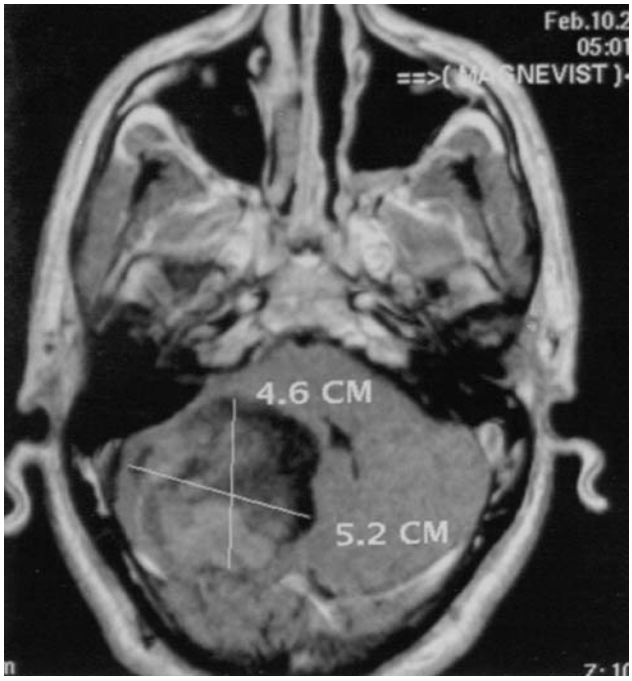

FIGURE 1. Showing MRI axial cuts of huge posterior fossa desmoblastic medulloblastoma.

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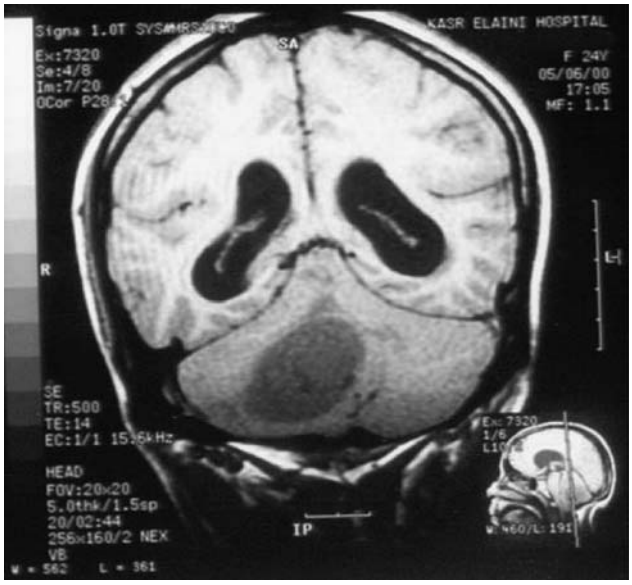

FIGURE 2. Preoperative MRI of posterior fossa medulloblastoma.

RESULTS

Patients had hydrocephalus underwent ventricular shunt procedures before surgical resection. Total resection was feasible in 8 patients (53.3%), subtotal resection (>50% removed) in 4 patients (26.6%) and partial resection (<50% removed) in 2 patients (13.3%). One patient (6.8%) had only biopsy and resection was infeasible, (Fig. 3). All patients received radiotherapy and 7 patients (46.7%) received 3 to 5 cycles of adjuvant chemotherapy in the form of cisplatin/vincristine/cytoxan/etoposide after surgery. Four patients received chemotherapy before radiotherapy and 3 patients after radiotherapy, (Table 4, Fig. 4). Histopathological examination determined 6 specimens (40%) exhibited desmoplastic histological features; 5 patients had lateral tumors and 1 had midline tumors.

TABLE 3. Modified Chang Classification for Medulloblastoma

T1	Tumor < 3 cm in diameter; limited to the midline vermis, roof of the fourth ventricle, or cerebellar hemisphere
T2	Tumor ≥ 3 cm in diameter, invading one adjacent structure or partially filling the fourth ventricle.
T3A	Tumor ≥ 3 cm with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing hydrocephalus
T3B	Tumor ≥ 3 cm invading brainstem
T4	Tumor ≥ 3 cm extending through the aqueduct of Sylvius to involve the midbrain or third ventricle, or down past the foramen of Magendie
MO	No metastatic disease
M1	Microscopic tumor cells in cerebrospinal fluid (cerebrospinal fluid cytology positive for tumor cells)
M2	Gross nodular seeding in cerebellar or cerebral subarachnoid space or in the third or lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Extraneural metastases

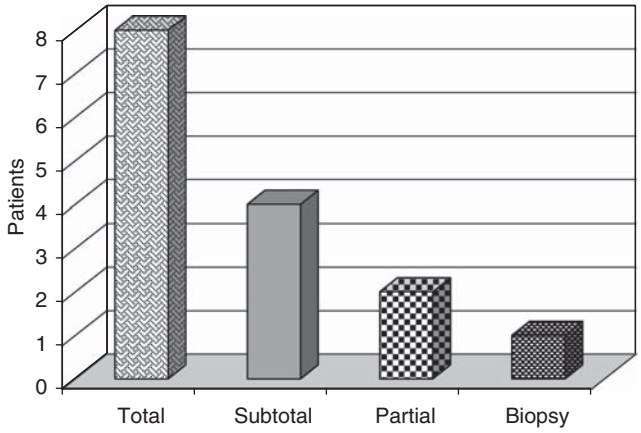

FIGURE 3. Patients' distribution according to the extent of surgical resection.

Radiotherapy was initiated after a mean duration of 40 ± 20; range: 15 to 90 days after surgery; patients received preirradiation chemotherapy started their radiotherapy after a mean duration of 52.5 ± 26.3; range: 30 to 90 days after surgery. The mean dose to the whole brain irradiation was 36 ± 5.2; range: 30.6 to 45 Gy and that to the posterior fossa was 55 ± 2.7; range: 52.0 to 60.4 Gy as 1.80 Gy/fraction for 5 fractions/wk. The median dose to the upper and lower spine was 30 to 36 Gy as 1.5 to 1.8 Gy/fraction, once daily. The median duration of radiotherapy was 60 ± 20.5; range: 36 to 111 days. Six patients required treatment interruption, 4 because of hematological toxicity and 2 because of nausea and vomiting, (Table 5).

The mean duration of follow-up was 36 ± 18; range: 6 to 72 months. Throughout the follow-up period patients were evaluated clinically and radiologically, (Fig. 5) and 5 patients experienced recurrences after mean duration of follow-up of 18 ± 12.5; 4 to 36 months. The posterior fossa was the most common site of recurrences, 3 recurrences were in the surgical beds and 2 as bone metastasis. Three of the patients had recurrence died as a result of the disease, whereas the remaining 2 were alive with persistent disease. Thus, the 3-year relapse-free was 66.7%, the 3-year morbidity secondary to recurrence 13.3% and the 3-year mortality secondary to recurrence was 20% persistent.

TABLE 4. Patients' Distribution According to Line of Management Undertaken

Extent of surgical resection	
Total	8 (53.3%)
Subtotal	4 (26.6%)
Partial	2 (13.3%)
Biopsy only	1 (6.8%)
Chemotherapy	
No chemotherapy	8 (53.3%)
Preirradiation	4 (26.6%)
Postirradiation	3 (20.1%)
Radiotherapy	
Number	15 (100%)

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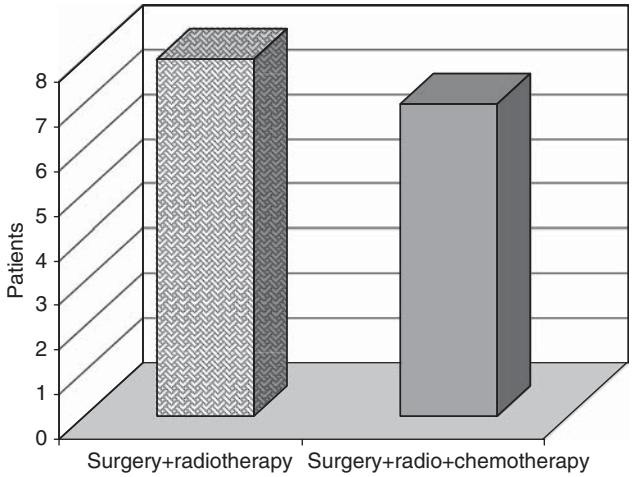

FIGURE 4. Patients' distribution according to the applied management policy.

There was a negative significant correlation between possibility of relapse and the extent of surgical resection, ($r = -0.660$, $P = 0.007$). Moreover, analysis of patients' demographic data, preoperative findings, extent of surgical resection, duration of radiotherapy, as predictors of relapse-free postoperative course using ROC curve analysis arranged these factors as following: the extent of surgical resection as the specific predictor, duration of radiotherapy, older age, male gender, lesion's pathological type, site of lesion, and duration of preoperative symptoms, (Table 6, Figs. 5, 6).

DISCUSSION

Patients had hydrocephalus underwent ventricular shunt procedures before surgical resection to relieve manifestations of increased intracranial tension and to safeguard against preoperative deterioration. Such policy goes in hand with *Muzumdar*[12] who reported that hydrocephalus is usually responsible for any sudden preoperative deterioration in the patient and it seems that treatment of significant hydrocephalus before an operation improves the patient's condition and subsequent clinical course.

TABLE 5. Radiotherapy Regimen Data

Timing of start radiotherapy after surgery (d)	
Irradiation after chemotherapy (n = 4)	52.5 ± 26.3 (30-90)
Irradiation before chemotherapy (n = 3)	38.3 ± 16.1 (20-50)
Irradiation only, no chemotherapy (n = 8)	34.1 ± 17.5 (15-70)
Total (n = 15)	40 ± 20 (15-90)
Duration of radiotherapy (days)	60 ± 20.5 (36–111)
Dose of radiotherapy	
Whole brain	36 ± 5.2 (30.6–45) Gy
Posterior fossa	55 ± 2.7 (52.0–60.4) Gy
Upper and lower spine	30-36 Gy as 1.5–1.8 Gy/fraction
Interruption of treatment	
No interruption	9 (60.1%)
Interruption because	4 (26.6%)
Hematological toxicity	
Nausea and vomiting	2 (13.3%)

TABLE 6. Stratification of Evaluated Parameters as Specific Predictors for Relapse-free Postoperative Course

Parameter	AUC
Extent of surgical resection	0.840
Duration of radiotherapy	0.740
Old age	0.660
Male gender	0.650
Pathological type	0.600
Lesion site (lateral or midline)	0.550
Preoperative duration of symptoms	0.500

Total resection was feasible in 8 patients (53.3%), subtotal resection in 4 (26.6%), partial resection in 2 patients (13.3%) and 1 patient (6.8%) had only biopsy and resection was infeasible. The extent of surgical resection indicated a fact that complete surgical cure could not be possible and that adjuvant therapies were mandatory, thus the applied policy of this study consisted of surgical resection as long as it is feasible with postoperative craniospinal irradiation and 7 patients received 3 to 5 cycles of postoperative adjuvant chemotherapy. Through a mean follow-up duration of 36 ± 18 months, 5 patients (33.3%) experienced recurrences, 3 recurrences were in the surgical beds and 2 as bone metastasis. Three of the patients had recurrence died as a result of the disease, whereas the remaining 2 were alive with persistent disease. Thus, the 3-year relapse-free was 66.7%, the 3-year morbidity secondary to recurrence 13.3% and the 3-year mortality secondary to recurrence was 20%.

The applied policy and reported extent of surgical resection were in line with that reported in literature; Greenberg et al[13] who treated 17 adult patients with medulloblastoma with surgery, craniospinal radiation plus local boost and adjuvant chemotherapy and found gross total resection was possible in 8 patients (47.1%), subtotal resection in 7 patients (41.2%), and 2 had partial resection (11.7%) and reported 2 relapsing patients during chemotherapy and 6 relapsed after completing all therapy with a relapse rate of 47.1% and mortality rate of 35.3% through a period of 56 months. Herrlinger et al[14] reported that in adult medulloblastoma after resection, 20 patients were treated with craniospinal radiotherapy and adjuvant chemotherapy and the median survival in the whole cohort was 126 months with the 5-year and 10-year survival rates were 79% and 56%.

Selek et al[15] used protocol of postoperative radiotherapy similar to that applied in this study and after a median follow-up time of 46.5 months found the 5-year actuarial survival rates for recurrence-free, disease-free, and overall survival were 82.5%, 73.5%, and 89.7%, and concluded that the current standard of care seems to remain craniospinal irradiation after maximal surgical resection of the primary neoplasm without clear indications for adjuvant chemotherapy. Brandes et al[16] found

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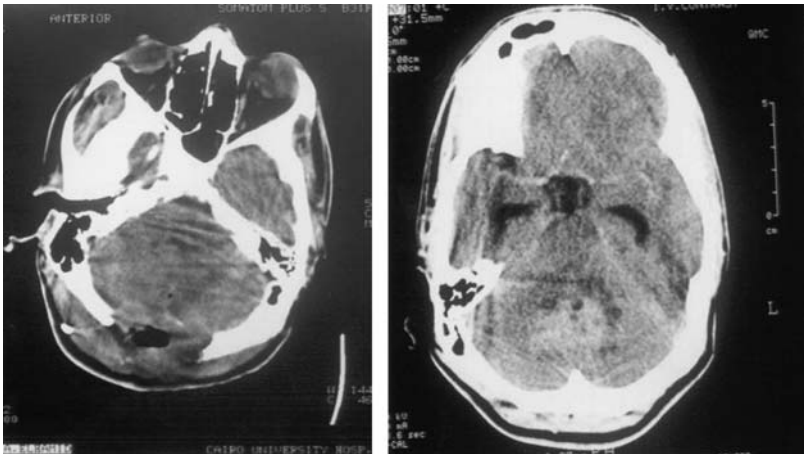

FIGURE 5. Preoperative and postoperative CT scan of posterior fossa medulloblastoma.

after a median follow-up of 7.6 years, among a total of 36 adults with MB, the overall progression-free survival and overall survival rates at 5 years were 72% and 75%.

Roldán et al[17] found the overall 5-year survival was 50% and tumor recurrence occurred 22.4 months after diagnosis and median survival after recurrence was 9.3 months. Menon et al[18] found total excision feasible in 13 of 18 patients (72.2%), near total in 4 (22.2%) and subtotal in 1 patient and adjuvant radiotherapy in the form of craniospinal irradiation with a posterior fossa boost resulted in 5-year survival rate of 55.5%. Also, Lai et al,[20] (2008), found the 2-year, 5-year, and 10-year relative survival rates were 79.9, 64.9, and 52.1%, respectively.

The completeness of surgical resection was found negatively correlated with the possibility of relapse and showed highest AUC as a specific predictor for relapse-free postoperative course and among demographic data, patient's age, and sex were predictors for treatment outcome, older patients have higher possibility of relapse-free postoperative course, whereas males have less favorable outcome. Such finding goes in hand with Rodriguez et al,[19] (2007), who reported that male sex was associated with decreased 10-year recurrence-free survival and overall survival. Menon et al[18] reported that adults fared better than children. Lai et al[20] reported that in multivariable regression modeling, age of diagnosis before 20, gross total resection, and radiation were favorable prognostic factors.

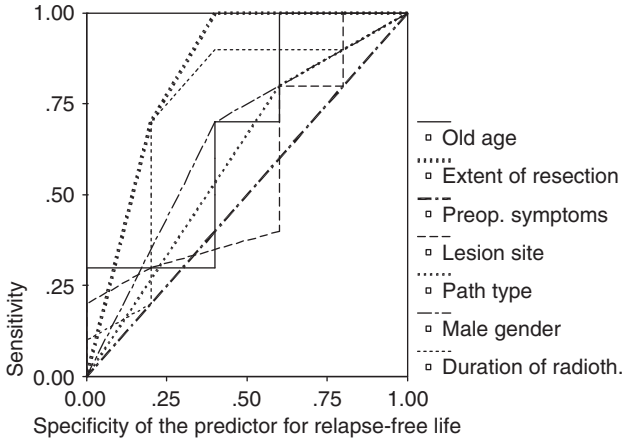

FIGURE 6. ROC curve analysis of studied parameters as predictors for relapse-free postoperative course.

CONCLUSIONS

It could be concluded that the assumed policy of surgical resection, as much as possible, followed by radio and chemotherapy was appropriate therapeutic modality for adult medulloblastoma with 3-year relapse-free life of 66.7%. The extent of surgical resection was found as a specific predictor for prognosis after such treatment policy.

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