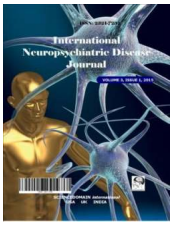

Internationa Neuropsychiatric Disease Journal
8(2): 1-8, 2016; Article no.INDJ.25411
ISSN: 2321-7235, NLM ID: 101632319

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Desmoplastic Medulloblastoma Patients Survival after Multimodality Treatment

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/INDJ/2016/25411
Editor(s):
(1) Zhefeng Guo, Department of Neurology, University of California, Los Angeles, USA.
Reviewers:
(1) Anonymous, University Of Calabarteaching Hospital, Nigeria.
(2) Arturo Solís Herrera, Human Photosynthesis® Study CenterHuman Photosynthesis® Study Center, México.
(3) Elaine de Guise, University of Montreal and McGill University, Canada.
(4) Neha Garg, Indian Institute of Technology, Mandi, Himachal Pradesh, India.
(5) Prashansa Agrawal, Case Western Reserve University, USA.
(6) Kurt Jellinger, Institute of Clinical Neurobiology, Vienna, Austria.
Complete Peer review History: http://www.sciencedomain.org/review-history/16202

Original Research Article

Received 1st March 2016
Accepted 7th September 2016
Published 15th September 2016

ABSTRACT

Aims: This is to investigate the results of the multimodality regimen including surgery, postoperative craniospinal irradiation and clarify the role of chemotherapy as well as the influence of multiple variables on desmoplastic medulloblastoma patient's survival.
Study Design: Original research papers.
Place and Duration of Study: It took place in the period between January 2001 and Sept 2015 at Neurosurgery and Clinical Oncology & Nuclear Remedies Departments of Mansoura university Hospital.
Methodology: We reviewed data of (28) patients histological confirmed as desmoplastic medulloblastoma (17 male beside 11 female) including clinical history, examination, investigation and management.
Results: The median age was 17.8 years, (range 3-41) with male to female ratio was (1.5:1). The

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most dominating symptoms were vomiting (82%) and throbbing headache (71.4%). The positioning of tumor was lateral in 64.3% and midline in 35.7%. The total resection of the tumor was achieved in 17 (60.7%) patients. All patients received craniospinal irradiation. The median dosage to the posterior fossa was 54 Gy (range 49- 56 Gy). 71.4% of the patients received adjuvant chemotherapy. The median follow-up was 52.3 months (range 25 -120). Five years' overall survival rates were 71.4% and 67.8% respectively.8 patients developed relapse. Posterior fossa was the commonest site for relapse (21.4%). Brain stem infiltration was bad prognostic factor (p= 0.006). The extent of surgical resection can be considered a good prognostic factor (p=0.004). Age, sex and tumor location did not significantly affect the results of survival. One of the most reported side effect was substantially, sensory neuropathy, nausea, vomiting, fever and neutropenia.

Conclusion: Patients with desmoplastic medulloblastoma being given chemotherapy adjuvant to surgical resection and radiotherapy (Multimodality approach) remain alive longer than patients who had management of surgery and radiotherapy only although brain stem infiltration, large post-operative residual are often associated with poor prognosis.

Keywords: Desmoplastic medulloblastoma; chemo-radiotherapy; end result.

1. INTRODUCTION

It is been postulated that Medulloblastoma could be the most frequent malignant embryonal brain tumor during childhood [1]. It accounts for 25% of brain tumor in children [1] that was assumed to originate from the neuroepithelial cells lining the roof of the fourth ventricle [2]. It is a highly invasive tumor with a tendency to disseminate early throughout the CNS. The current median age of diagnosis was at 5 a long time with 80% of cases which being diagnosed with the first 15 years of life. Often, it may consume as being a tumor of childhood; although it will probable occur in patients at any age that may comprises the elderly [3].

Medulloblastoma concerns in comparison to 3% of all adult primary central nervous system (CNS) neoplasm. It's cleared that 5-year survival rate designed for adult medulloblastoma have been improved lately and reach up to 80% [4-6].

Medulloblastoma have been categorized into several histological subtypes upright, desmoplastic and classical. Different variants associated with medulloblastoma include large cell, lipomatous, melanocytic and also medullomyoblastoma that are rare [7].

It turned out documented that, it could exist lots of difference between classical and desmoplastic variations such as the current age group linked with incident, site, cell involving origin, glial differentiation and DNA content [8]. The classical medulloblastoma occurred mainly in children at midline in location in 80%.

The desmoplastic medulloblastoma were regarded as a factor of good prognosis in comparison to the classical version which occurs more frequently throughout adult [9]. Sonic hedgehog (SHH) pathway activation constitutes a common feature linked with the genuine histologic subtype. [10] throughout children under 3 years, the desmoplastic medulloblastoma provides much better progression free survival (PFS) that gets to around 85% [11].

Childhood medulloblastoma was managed by surgery, radiotherapy for craniospinal axis as basic principle but adjuvant chemotherapy may be added. Common regimens used were cisplatin, lomistin as well as vincristin. Survival of patients received chemotherapy was greater than patient had radiotherapy only [12]. In adult patients, no official treatment strategy established. Almost all centers treat individuals inside pediatric protocols. Within children under 3 years, intensive chemotherapy is effective along with craniospinal irradiation to minimize the risk of neurological deficits.

This study retrospectively analyzed the experience (analysis of medical picture, radiological images, treatment result) of managing patients suffering from desmoplastic medulloblastoma at Mansoura university hospital in neurosurgery, medical oncology and nuclear remedies departments in addition to prognostic items impacting on patients survival.

2. MATERIALS AND METHODS

This study was completed retrospectively on 28 patients with histologically proved desmoplastic medulloblastoma (by H & E stain showed biphasic skeleton that contain areas of dense intercellular reticulin and nodules without

reticulin. Tumor cells show a neurocytic phenotype) whom admitted to medical oncology & radiotherapy in addition to neurosurgy on Mansoura School Hospital throughout period between January 2001 till Sept 2015. The patients who transferred to other hospitals, had multiple diseases, lost follow up early in the study or refused to share their information were excluded. The median follow-up was 52.3 months (range 25 - 120).

Data were collected and visualized using the patient's graphs pertaining for evaluation the analyzed items: Age, gender, age of presentation, essential imaging study like CT or MRI of the brain (Fig. 1), extent of operative resection, ventriculo-peritoneal shunt, utilization regarding chemotherapy or radiotherapy not only to the brain but neuroaxis also, total posterior fossa boost dose, chemotherapy regimen & dosage, surgery and radiation incase associated with relapse.

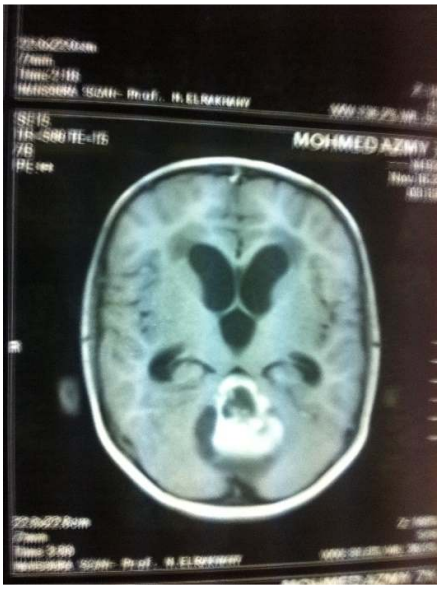

Fig. 1. MRI Brain axial cut T1 with contrast showed posterior fossa medulloblastoma

The craniospinal dissemination is becoming proved by CSF cytology and spine MRI results. This completed immediately after surgery. The extent of tumor resection was decided by the postoperative imaging and operative details registered by the surgeons. All patients underwent surgical resection followed by craniospinal irradiation after surgical recovery, most patients were managed by using a median dose of 34 Gy (range 23.4 - 36 Gy) radiation to the whole brain with booster dose to posterior fossa to reach minimum of 54 Gy (range 49 - 56 Gy) and 32 Gy (range 24 - 40 Gy) on the spinal axis.

The complete brain irradiation is usually delivered from two parallel opposing lateral fields which is matched up with the spinal field carefully. Posterior fossa boost was delivered via parallel-opposed photon beams. Craniospinal irradiation was given in susceptible location in prone spot and spinal irradiation was released by immediately posterior areas also field junctions were changed every a few sessions to have the ability to minimize the risk linked with overlap or simply under dose.

Twenty patients obtained every week vincristin VCR (1.5 mg/m2) and craniospinal radiotherapy then 6 to 8 cycles of cisplatin CDP (75 mg/m2), lomistin CCNU (50 mg/m2) on the same time that became repeated every six weeks. 8 patients did not obtain any sort of chemotherapeutic regimen.

The multimodality treatment protocol and ethical issue was confirmed by medical counsel's faculty staff in the departments which managed the patients.

Toxicity and tumor relapse were evaluated corresponding to the World Health Organization (WHO) standards [13]. Complete response (CR) are identified as complete disappearance of all the clinical and radiographic evidence of the disease at the time of evaluation. Partial response (PR) are described as >= 50% reduction of the lesion size with clinical improvement and stationary progression. Steady disease (SD) was described by lowering on the tumor size less than PR (≤ 50%) and a great increase for the tumor size less in comparison to progressive disease (PD) or might simply no response. PD are described Similarly >=25% increase in tumor size, or appearance of your new lesion. The patients followed -up in 4-6 weeks after finishing the regimen to check the response, toxicity along with disease condition. Subsequent follow-up was planned for every 3 months' regular intervals for the next two years then annually after that that.

Overall survival (OS) represented the whole time between the pathological identification and last documented follow-up or patient death. Progression free survival (PFS) was defined from the particular date of surgery until tumor relapse.

Relapse included, posterior fossa, the vertebrae, meninges in addition to extra neural sites (mainly bone). Regarding analysis Kaplan-Meier and SPSS techniques was used. We evaluate many variables to see if it is statistical significant as prognostic factors or not that include: Age, gender, tumor location, extent of surgical resection, brain stem infiltration in addition to radiotherapy dosage. Ideals **P <** 0.05 were considered to be as statistically significant.

3. RESULTS

Baseline patient's features are listed in Table 1. The median age group was 17.8 years. (Range 3 - 41 years) with male predominance (60.7%). Patients presented with various symptoms including headache, found in 71.4% of the patients. Other symptoms present was vomiting (82%), blurred vision (21.4%), and unsteadiness in 67.8% of the patients. Preoperative MRI was done for most patients. MRI proof brain stem infiltration was diagnosed in 5 cases (31.2%). Gross total surgical resection was achieved in 16 patients (60.7%), subtotal excision was achieved in 7 cases (25%). in 4 patients only, biopsy was done. Infiltration of the fourth ventricle was detected in 10 (35.7%) of the cases. CSF cytology have been completed in 96.7% of the patients, that was positive in single case 7.4%. The tumor was limited to the vermis in 10 patients (35.7%). it was solitary lesion in cerebellar hemisphere (lateral) in 18 patients (64.3%).

Twenty-two patients acquired standard risk disease (78.5%) identified as less than 1. 5 cm of tumor residual and no extension beyond the existing primary tumor. All 6 patients (21.4%) had the high risk disease, due to the occurrence of residual tumor more than 1.5 cm or proof of metastasis.

Most patients were given adjuvant craniospinal irradiation within increase towards posterior fossa. The median radiation dosage to posterior fossa was 54 Gy (range 49-56 Gy).

About 67.8% of the patients had been given weekly vincristin VCR (1.5 mg/m2) in the course of craniospinal radiation therapy subsequently 6-8 cycles of cisplatin CDP (75 mg/m2) in addition to lomistin CCNU (50 mg/m2) at the same time along with VCR (1.5 mg/m2) in time frame 1,8,15 and to be repeated every six to eight weeks, while 32.1% of patients did not obtain any kind of chemotherapeutic regimen.

Table 1. Clinical and treatment characteristics (n=28)

Age		
Median	17.8	
Range	3 – 41 y	
	No	%
Gender		
Male	17	60.7
Female	11	39.3
Symptoms		
Headache	20	71.4
Vomiting	23	82
Cerebellar symptoms	19	67.8
T stage		
T2	20	71.4
T3a	3	10.7
T3b	3	10.7
T4	2	7.1
M stage		
M0	26	92.8
M1	2	7.1
M2	0	0
M4	0	0
Risk category		
Standard risk	22	78.5
High risk	6	21.4
V/P shunt		
+ve	23	82.1
-ve	5	17.8
Surgery		
Total or near total	17	60.7
Subtotal	7	25
Biopsy	4	14.2
Post fossa dose		
> 50 Gy	19	67.8
< 50 Gy	9	32.2
Chemotherapy		
Yes	19	67.8
No	9	32.2
Tumor location		
Lateral	18	64.3%
Midline	9	35.7
Brain stem involvement		
+ve	5	17.8
-ve	23	82.1
CSF cytology		
+ve	2	7.1
-ve	25	89.3
Not done	1	3.5
Pattern of relapse		
Post fossa	6	21.4
Spine	3	10.7

The overall response rate (OAR) was 82.1% and complete response (CR) was 60.7% in addition to Partial response (PR) was 21.4%, whereas stable disease was in 17.9% of patients.

Adjuvant radiotherapy was perfectly tolerated by all patients with minor toxicity. The most frequently reported side effects include mild sensory neuropathy (10.7%), nausea, vomiting (21.4% of patients) and only three patients experienced febrile neutropenia throughout chemo radiation management.

The reported chemotherapy induced side effects were peripheral neuropathy (class 2) which was discovered in 9 patients (35.7%). Hypothalamo-pituitary dysfunction was registered in four patients (14.2%). Nine patients (32.1%) suffered relapse. Three patients experienced spinal metastasis or lost follow-up, while six patients got posterior fossa recurrence. 5-years progression free survival (PFS) was (67.8%), the median PFS was 60 weeks (Fig. 2).

The 5 years Overall Survival (OS) was (71.4%), median Overall Survival was 80 weeks (Fig. 3).

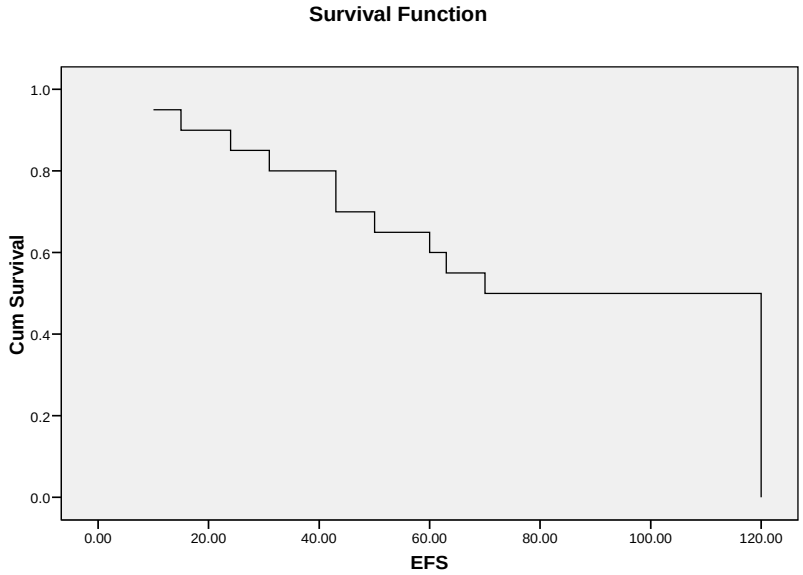

Fig. 2. Event free survival (EFS)

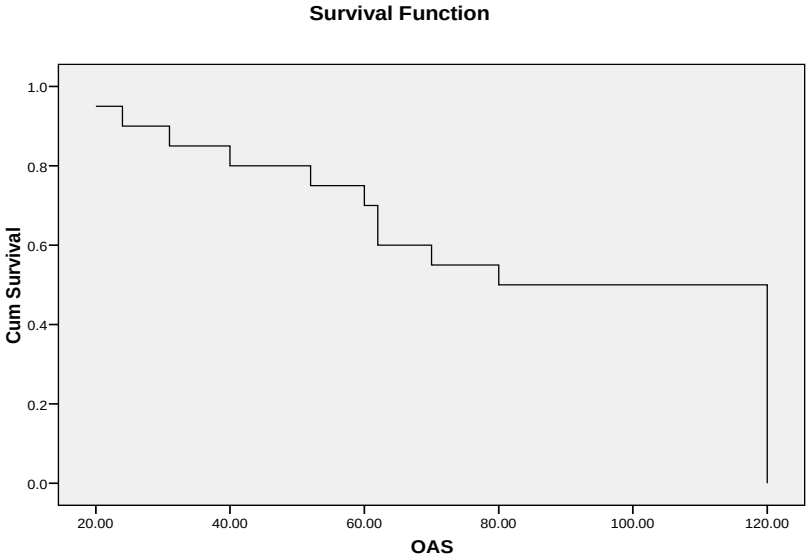

Fig. 3. Overall survival (OAS)

On the univariate, Kaplan–Meier and SPSS analyses associated with prognostic factors, progression free survival was found significantly better in complete surgical resection (p=0.004) along with higher radiotherapy dose on the posterior fossa (p=0.041) and administration of chemotherapy. Brain stem infiltration was correlated with poor prognosis (p=0.006). Age, sex, high risk group, and tumor location did not significantly influence the current treatment outcome (Table 2).

Table 2. Prognostic factors of progression free survival

Variable	P value
Age	0.050
Sex	0.696
Tumor location	0.806
Infiltration of 4 th ventricle	0.526
Brain stem infiltration	0.006
Extent of surgical resection	0.004 *****
Radiation dose to the post fossa	0.041*****
Metastasis	0.540
Risk category	0532

***** *= significant P < 0.05*

4. DISCUSSION

Mellulloblastoma might be a tumor of childhood. The tumor is usually less common in adult age, accounting of 1% of primary brain tumors, 80% occur at the end of your fourth decade [14-16]. Medulloblastoma may be categorized directly into desmoplastic/nodular. Medulloblastoma has extensive nodularity, anaplastic and large cell type. Desmoplastic type offers better prognosis and also is usually more common in adult [17].

In the retrospective study we checked clinical response, toxicity and also treatment end result for 28 patients with desmoplastic medulloblastoma. Most patients obtained craniospinal radiotherapy on other hand 67.8% of the patients had chemotherapy also. Overall survival (OS) was 71.4% and the five years disease free survival (DFS) was 67.8%. which resembling results were reported via Reiken et al. [1] may be to the similarity of the protocol.

In scientific clinical trial, patients who underwent complete or maybe near total resection and also had adjuvant chemo-radiotherapy achieved high OS and also DFS. We reported 5 years OS and also PFS was 83% and 80% respectively. These results comparable with Taylor et al. and Thomas et al. [18,19] data also which enhance the effectiveness of chemotherapy to alter the prognosis. Lots of researcher's s found indifference in results between patients that had or didn't receive chemotherapy [20]. In our paper, the presence of metastatic disease at the time of diagnosis did not significantly influence the treatment outcome which against what Packer et al. [12] conduct as patients with metastatic had poor prognosis. This is usually attributed towards small number of the patients whom presented by metastatic disease in our study and went with statement of Carrie et al. [21] who mentioned the administration of chemotherapy to these poor risk patients didn't improve the survival. Recently reviews found feminine gender as a better prognostic factor than male who had worse prognosis [21-23]. In our study, we did not find any prognostic value towards gender. This can be explained through the small number of patients that cannot reach statistical significance. Nag C, et al. [24] conducted a clinical trial of 25 patients, they reported 5 years and 10-years Overall survival rates (OS) 78% as well as 30% respectively. The median OS was 108 weeks in addition to median progression free survival was 63 months.

Other literatures reported OS rates (median 126 months; 5-years survival rate was 79%) and (median PFS 83 months, 5- year PFS was 56%) [25] several other series reported 5 year OR rate between 62% [5] and 83% [26] which comparable to our study due to nature of the disease and good regimen protocol for those patient in Egypt.

Brain stem infiltration or infiltration of the 4th ventricle consider as unfavorable prognosis. Brandes et al. and Padovani et al. [27,28] conducted this concept which also appeared in our research may be due to drop metastasis or due to limitation of radiotherapy doses to the brain stem directly which reduce the effectiveness of radiation. The administration of radiation dose towards posterior fossa (> 50 Gy) will enhance better prognosis that reported via Silverman and Simpson [29] may be due to effect of radiation on vascularity of the tumor or arrest of tumor cell duplication process.

5. CONCLUSION

Long term survival is possible in patients with desmoplastic medulloblastoma. Surgical excision in addition too postoperative craniospinal radiation and chemotherapy provide best results. Progression free survival found be significantly better with complete surgical resection along with

higher radiotherapy dose towards posterior fossa. Brain stem infiltration is correlated with poor prognosis. In our study, involving of adjuvant chemotherapy did not have better prognosis in adult patients. On other hand, adjuvant chemotherapy continues to be a powerful treatment tool after surgery in addition to radiotherapy throughout pediatric medulloblastoma patients. The addition regarding chemotherapy gives favorable results especially in risky patients, but this isn't statistically significant.

GUIDELINE FOR REPORTING *P* VALUES

In our paper we adopted *P* value significant if < 0.05.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16202