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Pediatric Medulloblastoma: A Study from Western Region of Saudi Arabia

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Abstract

Objective: Medulloblastoma is the most common malignant brain tumors in children worldwide. It is little known about the characteristics associated with medulloblastoma and the outcome in Saudi Arabia. Therefore, the study was conducted to understand the current status and what should be done for future.

Methods: A retrospective chart review of all children (<14 years) who have been diagnosed and managed with medulloblastoma at King Faisal specialist hospital and research center (KFSHRC) in Jeddah, Saudi Arabia from 2011 to 2017. Important epidemiological and clinical Data have been collected and analyzed through descriptive statistics to understand the clinical characteristics and treatment outcomes. In addition, Kaplan-Meier survival analysis was conducted to generate EFS and OS.

Results: The obtained results of OS of 73.7% with suggested that lower age (Age ≤ 3), high risk, positive metastasis at presentation, partial resection remained vital and contributed to lower overall survival rate among the patients with P value as follow: (P:<0.001, P:0.041, P:0.020, P:0.006). Moreover, event free survival rate was 54.8% and analysis of it suggested that the extent of complete surgical resection (P<0.018) and age >3 years (P<0.001) was the major factor for better survival.

Conclusion: As per the observation, the estimated outcome of total cohort was OS 73.7% and EFS 54.8% which are comparable to the developed countries. The age of > 3 years and the complete surgical excision are emerging as the most significant factors affecting OS (80.5%, 88.7%) and EFS (61.2%, 70%). Average risk and negative metastasis had significant OS with p value of 0.04, 0.02 respectively. This study provides an important clue in understanding the importance of the demographic, clinical, and treatment modalities in understanding the prognosis of medulloblastoma. This report will serve as an important resource from Kingdom of Saudi Arabia regarding medulloblastoma survival.

Keywords: Pediatric • Medulloblastoma • Embryonic Tumor • Malignant Tumors.

Introduction

Medulloblastoma in children is becoming a growing concern all over the world and with the growing number of reports; the disease is becoming a comparatively common embryonic tumor than a rare one with 20% of primary neuro/oncology malignancy seen in children [1]. Brain tumors and neuro-oncological conditions are comparatively less among the population. Yet, considering the number of patients suffering from various types of cancer, this small fraction has become quite large to have a serious concern. Medulloblastomas are predominant embryonal malignant tumors that have become a well-known form of neuro oncological disease condition from a rare form of the disease, especially in infants, children, and teenagers. McNeill reported that 9.3% of the pediatric CNS tumors are identified as medulloblastoma in the USA whereas all embryonal tumors account for 15% of the total cases [2]. Among the infants (Age 0-4 years), embryonal tumors are predominant. Recently, Lupo et al. [3] reported that the calculated annual incidence of the medulloblastoma cases ranges from 0.20 to 0.58 cases out of 100,000 populations. According to an earlier report, the number of cases was 1.5-2.0 per 100,000 populations, and most of the cases were recorded within 9 years of age [4]. Medulloblastoma is mostly originated from the posterior fossa region of the cerebellum and is considered as a Grade IV tumor with a high probability of metastasis through the cerebrospinal fluid (CSF). Apart from the common metastasis in the CNS, evidence of metastasis in other regions such as lymph nodes, viscera, and bone marrow have been reported [5,6].

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There has been an improvement in the survival of all groups over the past 20 years. A multimodality approach is the cornerstone of treatment. Post-surgical radiotherapy (RT) in combination with chemotherapy is considered as a standard of care for medulloblastoma in children. In 1970, randomized trials conducted by children cancer group and international society of pediatric oncology improved survival of high risk patients when incorporated adjuvant therapy. Current event free survival rates for high risk patients using full dose CSI with or without chemotherapy range from 30 to 74%. Most recent trials treating standard risk medulloblastoma using reduced dose CSI and adjuvant chemotherapy have produced EFS rates of 81 to 86% [7-9]. The reason for improved rates of survival are multiple and include improved postoperative care, possibly earlier or better detection of disease (especially disseminated disease), more aggressive surgery, improved radio therapeutic techniques and refinements in timing and dosing of chemotherapy [10]. Detail investigations by the researchers confirmed that the survival of the patients further depends on the subtype of the medulloblastoma. Till now, four major subgroups, namely, wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4, have been [11]. Analysis of the survival outcome of the patients based on these categories revealed that WNT type is having better survival outcome whereas as Group 3 is the most fatal type of medulloblastoma [12]. The present therapeutic and remedial options towards better survival of the patients largely depend on the targeted and effective surgical process along with other therapeutic interventions. Growing molecular understanding pertaining to the Hedgehog signaling pathways [13,14] and the origin of the disease condition allowed the medical practitioners to categorize and treat the condition precisely. Proper staging and risk stratification remains the key to better prognosis and patient outcomes.

The primary treatment in most of the cases is an integrated application of surgery and radiation therapy depending on the stage, localization, of the tumor and various patient associated factors including age. Often, ventricular shunt or ventriculostomy are opted either at the foramen of Luschka, and aqueduct of Sylvius depending on the necessity. Apart from surgery, various therapeutic interventions include radiation, chemotherapy and specific inhibitors for different signaling pathways associated with tumor development and growth. Postoperative cranio-spinal irradiation is effective for patients'

survival. Advancements in accuracy in targets through targeted volume delineation, optimization in the dosage and quality of the irradiation enabled to serve the patients better resulting in effective outcomes [15]. In parallel, to radiation, various modern chemotherapeutic approaches, and subtype-specific inhibitors are used as part of the treatment regime [16,17]. From Saudi Arabia, the number of reports on patient outcomes and survival related to medulloblastoma is limited. Countries such as Jordan and Saudi Arabia have been published pertaining to medulloblastomas [18,19]. The number of recent reports is limited from the Middle-Eastern countries including Saudi Arabia. This inspired us to share the valuable experience focusing on patient outcomes and survival.

Materials and Methods

This observational research study was designed to understand the patient survival and outcomes between January 2001 and December 2017 spanning an analysis of records of 16 years. International ethical norms for biomedical studies on humans were strictly followed for the present study. The study was approved by the Institutional Review Board (IRB) of King Faisal Specialist Hospital and Research Center-Jeddah (KFSHRC-J), Saudi Arabia (Approval Number: ONC-J/778/39, Dated: July 24, 2018). The data was collected from the Department of Oncology, KFSHRC-J. Being a retrospective study and involving patients' chart verification and analysis, no specific additional informed consent was required for the study. Data collected from the patient's medical records were collated and maintained at the Oncology Data Unit of the hospital following the institutional data protection and confidentiality policies. In this study, no data was retrieved in any form for any purpose without proper approval or permission from the appropriate individual or authority. As pre-decided prior to the study initiation, no identifying labels were used and the data made available to the investigators only on a need to know basis. As a retrospective study, this study was not associated with the patients' directly; hence, subjects of the study were devoid of any risk or health hazard. However, it is expected that the outcome of the study will definitely benefit the patients in the future.

Data collection, processing and management

All data collection was done on a standard case report form (CRF), and the medical details for the patients requested from the medical records department were extensively reviewed before considering. Data pertaining to the patient demographic information such as age, and sex, presenting clinical symptoms and signs, disease stage and treatment regime followed including surgery type, chemotherapy, radiotherapy, and specific response to the treatments and associated therapy-related toxicity were considered.

Inclusion and exclusion criteria

All medulloblastoma patients less than 14 years of age from 2001 till 2017 who confirmed their diagnosis in the pathology lab were included. Patients' information with missing data and the patients who did not receive throughout stay for the completion of their respective therapies, whether radiotherapy or chemotherapy, was excluded from the present study.

Patient data stratification

A total of 53 patients were planned to enroll in this study. No data were available for four patients; therefore, data were scrutinized for 49 patients. However, 8 patients did not receive complete mainstay and therapy as per the study design. Hence, the per-protocol final dataset contains 41 patients. Analysis of the clinical presentations was done for each patient carefully. The collected data were scrutinized extensively before any statistical analysis. Further, the complete dataset was grouped into standard patient information and high-risk patient data based on vital parameters such as the age of the patient during diagnosis, degree of surgical resection, metastatic status.

Treatment regime

All the patients underwent surgical interventions with the intent of maximal where maximal surgical resection was intended for each case. For the patients having age ≥ 3, and posing an average risk, complete or near-complete resection opted through surgery, followed by craniospinal irradiation (RT), and subsequently, adjuvant chemotherapy also opted. These children were treated with 36 Gy of craniospinal RT after surgery, followed by a posterior fossa boost of 18 Gy, therefore, a total RT dose of 54 Gy was applied to the tumor bed. The children received vincristine weekly during RT (a total of 5 doses were used). After completion of RT, patients received six to eight cycles of chemotherapy (vincristine and cisplatin, and CCNU). For patients with high-risk disease conditions of the same age, the dosage of radiation was differently considered. Postoperative craniospinal RT of 36 Gy was used, continued by a posterior fossa boost of 19.8 Gy. Thus, making the total dosage of RT for the entire tumor bed to 55.8 Gy. So, most of the patients have received posterior fossa boost with recent exception of 4 patients who received VMAT technique. Similarly, the weekly dosage of vincristine was given to these children as well as radio-sensitizer. The post-RT chemotherapy cycle for these patients was eight cycles each where vincristine, cisplatin, and CCNU opted.

Those patients with medulloblastoma, who were younger than 3 years of age, were subjected to baby brain chemotherapy protocol after the surgery. This protocol contained a total of six segmented 12-week courses with a total of 72 weeks course. The course consisted of 3 cycles A, A2 {Cyclophosphamide, VCR}, and B {Cyclophosphamide, VCR and Cisplatine}. The RT deffered in these cases and they were offered 36 Gy of craniospinal RT and later on, a posterior fossa boost of 18 Gy, thus, a total dosage of 54 Gy was administered to the tumor bed. This dosage opted for those patients who were having progressive or residual disease conditions or those who relapsed after a year of chemotherapy completion.

Statistical analysis

The sample size for the analyses was identified by the total population sampling and a consecutive sampling technique was considered for sampling the dataset having information from 2001 to 2017. In this study, all continuous data points are presented as median with minimum and maximum values. Kaplan-Meier curves were developed and analyzed for survival analysis and were rigorously verified for any difference between the survival times using the Breslow test in a univariate setting. Following the common statistical assumptions, a P-value of <0.05 was considered as statistically significant.

Results

A total of 41 patients were considered for this study where the typical clinical presentations suggested that 89% of the patients were having vomiting, 85% of the patients presented various degrees of headache, ataxia was observed in 67% of the patients, and cranial nerve defect was recorded in 20% of the patients. Males were predominant to females with 66% (27) compared to 34% (14) females, giving male to female ratio of 1.9:1. For the cohort median age at diagnosis at KFSH & RC-J was 7.1 years (range from 0.5 to 13.2) 5.9 years among boys and 8.3 years in girls.

Table 1: Presentation of the observation of follow-up time, time to death, and relapse time.

	Follow-up time (Yrs.)	Time to Death (Yrs.)	Time to relapse (Yrs.)
Mean	5.56	1.98	1.43
Median	4.98	0.93	1.28
Minimum	0.22	0.22	0.17
Maximum	17.03	7.04	4.64
Std deviation	4.22	2.08	1.09

Table 1 presents the statistical description of the observation of the follow-up time to death, and relapse time of the patients. The outcome is presented as mean ± standard deviation (SD). The mean follow-up time was around 5.56 ± 4.22 years, and the time to death was 1.98 ± 2.08 years, whereas the mean relapse time noted was 1.43 ± 1.09. The observed minimum follow-up time was as low as 0.22 years and the maximum follow-up time was 17.03 years. The median relapse time was noted as 1.28 years, therefore, a strict follow-up to check probable relapse should be conducted just after a year of the chemotherapy completion, as the present data suggests.

Here, 27 patients (66%) had total resection, 5 (12%) had near total resection and 9 (22%) subtotal resection. As the sample size is considered to be small, we decided to compare as two startum based on complete surgical excision to group complete and partial include (near total and subtotal) resection, 66% (27) had complete resection while 34% (14) had partial resection.

We look at that interval between the time of surgery till time of starting of radiotherapy and. We found it was not clinically significant in overall survival with p value: 0.769 (Breslow).

Treatment related side effects have been addressed in this study and classified based on Common Terminology Criteria for Adverse Events (CTCAE) version 5 and it is found that 53% of patients developed hearing toxicity which exceptionally graded by (SIOP Boston Reference) majority was grade 1 and grade 2; only 9% was grade 3 (2 patients), followed by 36% had growth hormone deficiency, 34% hypothyroidism, and only 2% had nephrotoxicity. For the cohort of patients, we divided patients into following risk stratification. High risk patients were those who had more than 1.5 cm2 post resection residual disease, and/or with M1-M4 distant metastases, rest of them all were classified as standard risk. With this, we had 24 (59%) with high risk disease and 17 (41%) standard risk. A five-year overall probability of survival analysis was conducted for the medulloblastoma patients using Kaplan-Meier estimates. The results of the five-year survival estimation are presented in Table 2. Analysis were conducted for the age at diagnosis (greater or lesser than age 3), gender (male, female), metastatic status at presentation (negative, positive), surgery type (gross total resection, near-total resection, and subtotal resection), and risk groups (high, standard risk). The five years overall survival for the whole cohort of the patients was 0.737 ± 0.072 (73.7%) Upon further investigation using Kaplan-Meier estimator analysis for overall survival, five year overall survival for patients diagnosed ≤ 3 years after birth, was significantly poor (0.333 ± 0.192) as compared to those with > 3 years (0.805 ± 0.072), P-value: <0.001, Figure 1A). Patients who underwent complete surgical resection do better survival than partial surgical resection patients (0.700 ± 0.089 *vs*. 0.241 ± 0.120, p value = 0.018, Figure 1B). The same for average Risk patients 41% (n = 18) was 0.944 ± 0.054 as compared to 0.591 ± 0.106 for 59% (n = 24) High Risk patients (p-value = 0.041, Figure 1C). Twenty two of the patients (45%) who presented with non-metastatic disease fared better than those 19 (46%) with metastatic disease in terms of five years overall survival (0.886 ± 0.078 *vs*. 0.570 ± 0.115, p value = 0.020, Figure 1D). We found that the overall survival in respect to gender was not significant with p value of: 0.444 (Breslow) in Table 1. Figure 1 represents the observed overall survival observed with reference to the demographic and clinical parameters such as age group (Figure 1A), types of surgery (Figure 1B), Risk group (Figure 1C), and metastasis (Figure 1D).

While the progressive disease rate was 44% (18 of 41), the 5-year event free survival for the cohort was 0.548 ± 0.080 (54%). The observation suggests that the cumulative survival of the whole cohort could extend more than 17 years. The age-wise analysis revealed that survival chances are more in case of patient age >3 years. The cumulative survival can be up to 17 years in case of age >3 whereas, for patients with age ≤ 3, the cumulative survival is only around 7 years (Figure 2) with significant p value. Risk group dependent analysis revealed the obvious expectation where the average-risk group displayed comparatively better cumulative survival in comparison to the higher risk group (Figure 2). As expected, patients age group > 3 years was better in progression free survival than < 3 years of age 0.612 ± 0.085 vs. 0.167 ± 0.152 (p-value = 0.001 Figure 2A), patients who underwent complete surgical resection were better than who underwent partial surgery 0.700 ± 0.089 *vs*. 0.241 ± 0.120 (p-value = 0.018) Figure 2, B, Risk stratification and metastatic status assessed during the initial clinical investigation, represents the cumulative survival outcome of the patients in relation to the metastasis and risk shown significant better progression free survival outcome observed for the patients having Average risk and negative metastatic presentation, However it was not statistically significant. Figure 2C and Figure 2D. Gender found to be not a significant factor in determining the event free survival with p value of: 0.085 (Breslow). As mentioned earlier, survival analysis was conducted with the specified statistical measures for the collected data in this study. The cumulative survival time was estimated with reference to event-free survival (EFS) in years considering multiple demographic, clinical, and pathological parameters considered in this study. Figure 2 represents the observed event-free survival observed with reference to the demographic and clinical parameters such as age group (Figure 2A), types of surgery (Figure 2B), Risk group (Figure 2C), and metsiasis (Figure 2D). Further Logistic Regression analysis was done and showed types of surgery and status of metastasis playing the major role in the survival of the cohort with p value: 0.002 and 0.040 respectively (Table 3).

Table 2: Kaplan-Meier estimates of cumulative probability of five-year overall survival of medulloblastoma patients.

Clinicopathological characteristics	Five-year overall survival	P-value*
Age at diagnosis, years		
≤ 3	0.333 ± 0.192	<0.001
> 3	0.805 ± 0.072	
Gender		
Female	0.774 ± 0.115	0.444
Male	0.724 ± 0.090	
Metastatic status at presentation		
Negative	0.886 ± 0.078	0.02
Positive	0.570 ± 0.115	
Surgery Type		
Gross Total Resection	0.887 ± 0.061	0.009
Near-Total Resection	0.800 ± 0.179	
Sub Total Resection	0.333 ± 0.157	
Risk group		
High risk	0.591 ± 0.106	0.041
Low / standard risk	0.944 ± 0.054	
* Breslow (Generalized Wilcoxon)		

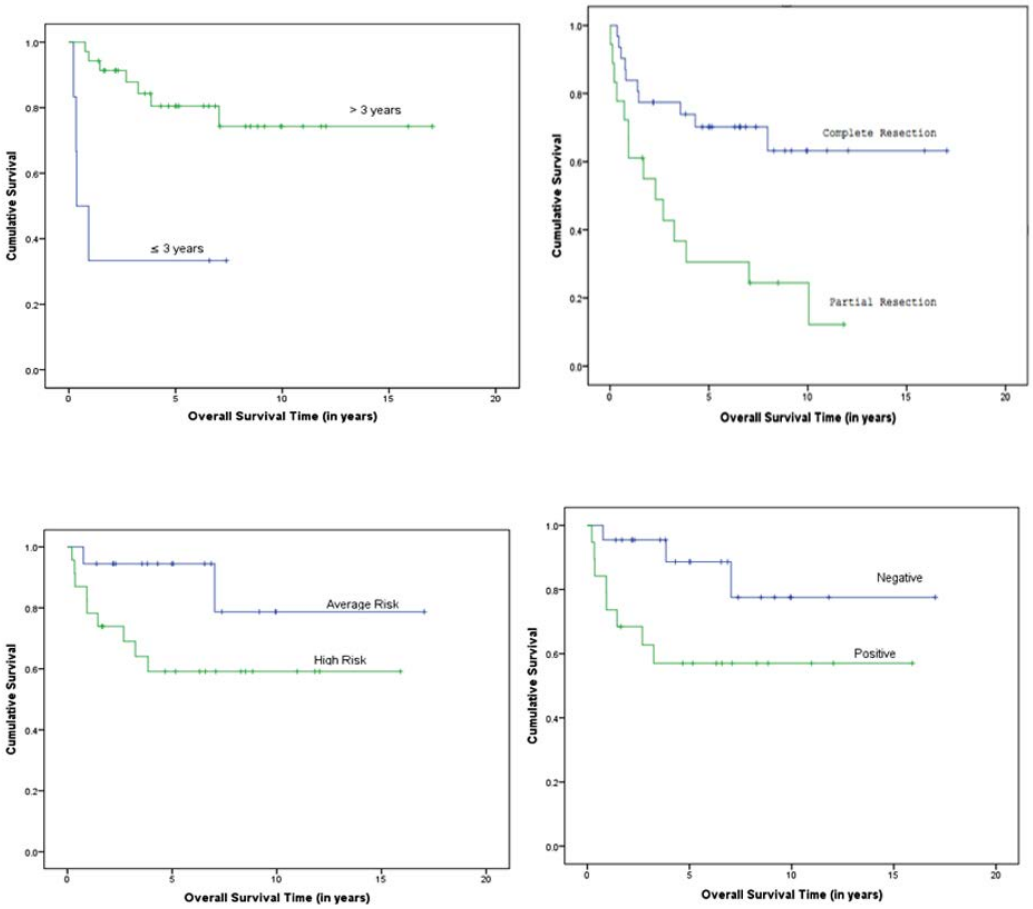

Figure 1. Estimation of cumulative overall survival (OS) in years with respect to the age group, surgery types, risk group and metastasis.

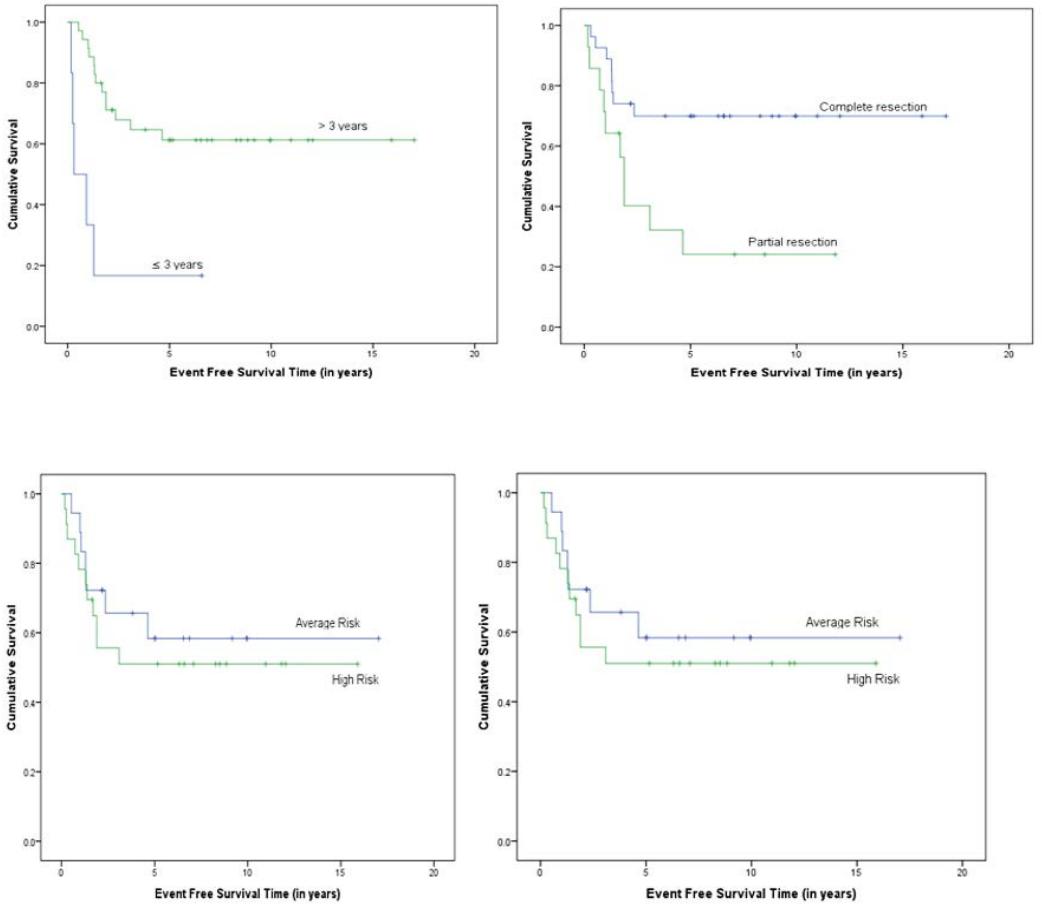

Figure 2. Estimation of cumulative event-free survival (EFS) in years with respect to the age group, surgery type, risk group and metasiasis.

Table 3: Logistic Regression analysis.

Variables not in the Equation			
Variables	Score	df	Significance
Age	1.864	1	0.172
Gender (1)	0.316	1	0.574
Metastasis (1)	4.209	1	0.04
Surgery (1)	9.951	1	0.002
Overall Statistics	13.359	4	0.01

Discussion

Children within the age group of 5 to 9 years are most vulnerable to Medulloblastoma. The observed ratio of male to female is 1.7: 1.0 [20]. The information of the Saudi cancer registry of 2014 suggests that 8.9% of the Medulloblastoma patients were male compared to the 7.9% female patients. The present study was having almost similar male to a female patent ratio of 1.9:1. Moreover, 14% of the patients were under 3 years of age. A higher level of metastasis was observed in 46% of the patients whereas 59% of the total patients displayed higher risk stratification. Following the global treatment regime and assessing the patients' disease condition, 66% of the patients were subject to complete surgery. 73% of the patients were able to survive and 27% of the patients (11 patients) died. Out of these 11 patients, during treatment, progression was observed in 4 patients and 6 relapsed after treatment and 1 patient was infected with septicemia. Overall survival in average risk is 94% while event free survival in this group is 58% that can be explained by loss of some patients follow up in this group. The conducted survival analysis of 5 years as presented in the result section showed that total events were 11 (27%) out of 41 patients, the overall of the whole cohort was around 73%. Analysis of the success rate of the surgery type suggested that 3 events occurred out of 27 for the complete resection whereas partial resection 14 patients resulted in 8 events. The success rate of complete resection was statistically significant (P = 0.006, Breslow). Hence, for better patient survival complete resection is suggested if the clinical conditions are found appropriate. Similarly, we observed negative metastasis increases the survival chances as presented in the result section. The age-based overall survival analysis indicated that patients with more than 3 years of age (80%) displayed better survival outcomes compared to patients with less than 3 years (33.3%). Analysis and identification of the factors that are crucial for the survival of the patient should be on top priority so that the effective treatment regime can be developed and the survival rate can be increased [21]. Our observations reported that the average survival rate is around 70% in cases of Medulloblastoma. We achieved comparable outcome in our report 73.7%.

In our study, the five year overall survival for standard risk vs. high risk patients was 94% vs. 59% (P = 0.041). A randomized North American study (Paediatric oncology group POG 9031) showed 76.1% overall survival in high risk medulloblastoma patients who received radiotherapy before chemotherapy which is the best study for high risk so far [22]. The result showed 7.2 years overall survival of high risk patients of medulloblastoma as (PENT3) was 50.0%. Comparing our results to the previous two studies we found that our results fall in between those two international studies.

Packer et al. (2013) reported (Children oncology group trial A9961), 5 year overall survival in standard risk was 87% that found to be 94% in our study [23]. Metastatic stage is among the well-known clinical characteristics of prognostic significance. Many studies have reported presence of dissemination at diagnosis as dominant prognostic factor [24,25].

The survival rate with metastatic disease was not higher than 30-40% [26]. Five year overall survival for non-metastatic disease vs. metastatic disease in our study was 84% vs. 63% (P = 0.020). We found that there was no statistically significant difference for overall survival between gender. Other studies also showed no disadvantage for boys as well [24].

Ufuk Ab et al. reported the time interval between surgery and radiotherapy was a significantt prognostic factor, wheras Jenkin et al. (2000) reported that interval between surgery and RT did not show a detrimental effect of a delay in treatment results for pediatric or adult medulloblastoma patients which is in agreement with the treatment results evaluated in our study [27].

Adjuvant therapy anchored by the use of alkylators, platinators, and microtubule inhibitors. It has made a significant impact in the survival of pediatric medulloblastoma. Chemotherapy may cause serious side effects like Cisplatinum which is the corner stone of our chemo regimen back bone in medulloblastoma and commonly used for children with medulloblastoma which frequently results in some degree of hearing impairment and may impact on quality of life that was similar to what we found in our study [28].

This report, although limited, provide great insight about where we stand now in management and outcomes of medulloblastoma in Western province of Saudi Arabia. Our analysis and the interpretations are in accordance with the earlier report [29] where they have emphasized that the patient outcomes are dependent on the patients' age and the extent of disease. Risk stratification is considered vital in treating medulloblastoma patients [30]. Our present analysis suggests that apart from risk assessment based on the medulloblastoma classification, the patient's age, the extent of the disease condition, and stage of metastasis should be given primary importance during diagnosis and determining the treatment regime. There are several drawbacks of this study; these include the retrospective nature, relatively small size, single center, no molecular data and lack of central review. However, the present analysis can serve as a valuable reference for future analysis to determine the essential survival factors, especially for the Kingdom of Saudi Arabia.

Conclusion

The study has shown encouraging outcome results of childhood medulloblastoma which is approaching the developed countries rate. Such results have been achieved through collaborative effort from different specialties including pediatric oncology, neurosurgery and radiotherapy teams. The data has confirmed the critical role of achieving complete surgical resection. Concurring with other reports, partial resection, metastasis and younger age (<3) are poor prognostic factors.

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