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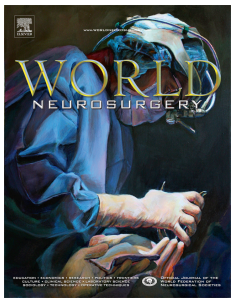

Are the Radiological and Molecular Features of Pediatric Medulloblastomas Valuable Prognostic Indicators? A 10-year Retrospective Review in the Middle East.

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ABSTRACT

Background: Medulloblastomas are the most common malignant brain tumors in the pediatric population. Based on the idea that tumors with identical radio-genomic features should behave similarly, the four molecular subtypes are now widely accepted as a guide for the management and prognosis. The radiological features of medulloblastomas can predict the molecular subtype; thus, anticipating the subsequent disease progression. However, this has not been evaluated comprehensively.

Purpose: We aim to thoroughly study the association between the molecular subtypes and radiological features of medulloblastomas. Moreover, we aim to investigate the efficacy of this correlation with the use of progression-free survival (PFS) and five-year survival rates.

Methods: A retrospective analysis was conducted for all histopathological confirmed medulloblastomas in pediatric patients (<16 years old) that were operated on in Kuwait over the past ten years (n=44). The radiological, histological, and molecular characteristics were justifiably evaluated and analyzed in our sample.

Results: The overall progression-free survival after one year was noticed among 27 cases (≈44%) and the non-specific five-year survival was seen in 31 cases (≈70%) after a five-year follow-up. SHH and WNT had the best outcomes, while group 3 showed the worst outcomes.

Conclusion: Our findings did not support the association between most of the typical MRI characteristics and survival rate. We further established that SHH and WNT biological types have a better prognosis. There was no association observed between the radiographic features, specifically the location, and the molecular subtype.

Word count: 236

Key words: Medulloblastoma, Molecular features, Radiological features, Progression-free survival, five-year survival

Abbreviations:
MRI: Magnetic Resonance Imaging
NOS: Not Otherwise Specified
PFS: Progression-free Survival
SHH: Sonic Hedgehog
WHO: World Health Organization
WNT: Wingless

INTRODUCTION

Medulloblastoma is the most common intracranial malignant brain tumor that predominantly affects children [1]. While the cause of medulloblastoma is unknown, certain genotypes have been identified to confer an increased risk of this tumor [2]. Though brain tumors have always been classified based on histology, the fifth edition of the World Health Organization (WHO) 2021 restructured this classification based on the molecular parameters in addition to its histology [3]. This grouping serves as a guide for management decisions based on the idea that tumors with similar genotypes will behave in a similar manner [4, 5]. The current biological stratifications consist of four known molecular types and clinical variants, including Wingless (WNT), Sonic Hedgehog (SHH), group 3, and Group 4 [6, 7]. Indeed, WNT and SHH medulloblastomas disclose modifications in the corresponding signaling pathways (i.e., WNT groups are driven by CTNNB1 gene mutations encoding b-catenin, while SHH groups have somatic mutations of PTCH, SMO, and SUFU genes) [8]. While groups 3 and 4 medulloblastomas are not categorized by any exact oncogenic alterations [6, 7]. Additionally, it is relevant to mention that the clinical and survival behavior of medulloblastomas varies with the distinct molecular pattern rather than the histological appearance. Principally, group 3 medulloblastomas carry the worst prognosis, and SHH and group 4 medulloblastomas seem to have an intermediate prognosis [6]. On the other hand, children younger than 16 years with WNT type have been shown to have a favorable prognosis [6].

Several publications suggest that the radiological features of medulloblastomas (i.e., the location of the tumor) can predict the molecular type [9]. Hence, anticipating the prognosis and subsequent management before any intervention. However, this has not been extensively studied and is a novel topic of debate. The current multimodal management strategies, involving maximal safe surgical resection, radiotherapy, and chemotherapy, have improved the overall survival rate [10]. Several clinical trials have emerged to balance the complications of treatment, especially for high-risk groups, while also maintaining an excellent prognosis [11, 12]. The five-year survival rate after treating medulloblastoma varies worldwide and could be lower for those living in areas without ideal neurosurgical and oncological resources. The clinical connotations of the molecular subtypes present a unique challenge for countries with no reported data [13]. In the Middle East, there has only been a single published abstract to date, which describes the survival rate of such patients about their genomic subgroups in 55 pediatric patients [14]. Our paper is the first study to emphasize the radiological characteristics and the second study to speak about the genomic types for medulloblastomas and their impact on treatment and prognosis in the Middle East region.

This retrospective study reviews a 10-year data sample in Kuwait of Pediatric Medulloblastomas and discusses the relationship between the radiological features, molecular subtypes, and long-term outcomes. Our rationale was to investigate whether an association exists between the molecular subtypes and radiological features, as this subject is still under scrutiny. For those with available molecular data, we investigated its alliance with the radiological characteristics with the use of progression-free survival (PFS) after one-year and five-year survival rates.

METHODS

Study design and Participants:

Our study design involved enrolling all pediatric patients (less than or equal to age 16 years) with posterior fossa tumors with a diagnosis of medulloblastoma that had been operated on in our center (Ibn Sina Hospital, Kuwait). Patients who remained in Kuwait for adjuvant treatment were either stratified as low-risk or high-risk protocol. The period of enrollment ranged from January 2010 until December 2021. Our inclusion criteria comprised every patient with a confirmed histopathological diagnosis of medulloblastoma after surgical intervention. Exclusion criteria included all adults over the age of 16 years and those without a confirmed histopathological diagnosis. We utilized the histopathological and surgical databases of our center to select the subjects. This study represents all the cases that underwent a posterior fossa craniotomy for tumor resection at our institute, which is the only center that manages generalizability to the target population in Kuwait.

The samples were re-evaluated histologically by a board-certified neuropathologist, following the 5th edition of the WHO classification of tumors of the central nervous system (2021). The Hematoxylin and Eosin (H&E) stained slides have been re-evaluated along with their immuno-stains and special stains that contain synaptophysin, GFAP, b-catenin, P53, and reticulin. In addition, a GRB2-associated protein 1 (GAB1) immuno-stain was performed. The cases with available paraffin blocks have been sent to a certified molecular pathologist for further methylation. An oncological multidisciplinary review of all the cases including radiological features before proceeding forward with the standard or high-risk treatment was performed.

Each patient with medulloblastoma was then followed from the records for at least five years or to death. The primary endpoint for our cohort was progression-free survival (PFS). Furthermore, the overall five-year survival was applied as the secondary endpoint.

Ethical Consideration:

The ethical approval for the conduction of this study was verified by the Standing Committee for Protection of Human Subjects in Research from the Ministry of Health in Kuwait. The data were retrospectively reviewed using the medical records. This study followed the research ethical standards that respect the confidentiality and privacy of the participants.

Data Collection Method:

A convenient sampling method was applied for our data collection. They were classified based on age categories (i.e. categorized on the ability to receive radiotherapy and adolescent age), gender, radiological features (location, enhancement pattern, as well as the presence of hemorrhage, calcification, cystic component, and hydrocephalus), year of intervention, metastasis at the time of presentation, the extent of surgical resection (near total resection (NTR) or gross total resection (GTR)). In addition, the stratification was divided according to the histopathological class (classic, desmoplastic/nodular, large cell-anaplastic), molecular type (Wingless (WNT), Sonic Hedgehog (SHH), group 3, and group 4).

DNA Methylation Profiling of the Cohort:

The methylation array used was the 450K-array analysis or EPIC (850K) to extract the genomic findings from formalin-fixed paraffin-embedded samples. This was done according to the manufacturer's instructions (Illumina). In addition, Copy Number Variation analysis was performed. Molecular characteristics of the WNT subgroup (CTNNB1 mutations, chromosome 6 loss), MYC and MYCN amplifications, and chromosome 17 status were investigated. A Random Forest Classifier was generated, which calculated the class probabilities from the resulting scores.

Statistical Analysis:

The information was analyzed via the IBM Statistical Package of Social Sciences (SPSS). The qualitative variables were summarized into frequencies and percentages. The null hypothesis was rejected using Pearson's Chi-square. An equal distribution between the groups was ensured before the analysis to reduce the confounding effect. The association of our variables (age, gender, radiological features, metastasis, year of intervention, the extent of resection, molecular test type, receiving radiotherapy, and chemotherapy treatment risk) was tested and a p-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 44 patients were stratified based on demographic characteristics, radiological features, histological, and genetic types. Furthermore, patients were classified in terms of the

extent of surgical resection and the treatment risk, being standard or high. The median age was 6.5 years with the range being from one year to 16 years old. Table 1-a depicts that five patients (11%) were less than 3 years old; 27 (61%) patients were between the ages of 3 and 9 years, and the remaining 12 patients (27%) were between the ages of 10 to 16 years old. Most of the patients (70%) were males.

As shown in table 1-b, most of the posterior fossa medulloblastomas in our sample were located in the midline (70%). Around 23% of cases developed intra-lesional hemorrhage and 34% showed calcification. As expected, most of our samples (95%) demonstrated enhancement with gadolinium contrast. Moreover, we found that 11% were solid, 34% were cystic, and the majority, 55%, were mixed (solid and cystic components). Most of the cases (95%) developed pre-operative non-communicating hydrocephalus.

As per the latest WHO genetic classification of medulloblastoma, table 1-c revealed that around 25% of medulloblastomas in our sample were sub-grouped into group 4 subtype. Seven percent were categorized under group 3 molecular subtype. Respectively, the WNT category, which is known to have a better prognosis comprised 11%, and SHH contributed 23% of our sample. Table 1-c further depicts that 61% of tumors were genetically methylated with the remainder being unmethylated. As anticipated, most of the histopathological examinations revealed the classic and the desmoplastic/nodular sub-types (Table 1-c).

Table 2 indicates the association between different characteristics and the progression-free survival (PFS) after one year of follow-up. The highest PFS was among males between three and nine years of age; however, both age and gender were not statistically significant. Concerning radiological features, interestingly, only Gadolinium contrast enhancement showed to be associated with a higher PFS ($p = 0.047$). All the remaining radiological attributes were non-significant. With respect to molecular subtype, a significant association with PFS was noted in the analysis ($p = 0.042$). Cases exhibiting the SHH molecular subtype had the best PFS (50%) while group 3 had the worst with only 7% achieving the PFS after one year of follow-up. The extent of surgical resection also demonstrated an association ($p = 0.019$). Additionally, cases who were treated by a combination of surgery and radiotherapy, and chemotherapy experienced a favorable PFS (65%); however, this association proved to be statistically non-significant in the analysis.

Table 3 represents the association between our multiple variables and our secondary endpoint (the five-year survival rate). Like the PFS, only Gadolinium contrast enhancement was associated with a higher five-year survival ($p = 0.050$). There is no prediction of the secondary outcome by the other features. The molecular subtype demonstrated a statistically significant association with the five-year survival rate ($p = 0.039$). Similar to the PFS, the SHH subtype was associated with a better prognosis in our sample with a high five-year survival rate of 42.2% while

group 3 had the lowest prognosis. Treatment with gross total resection also proved to be statistically significant. Patients treated surgically with gross negative tumor bed margins exhibited a superior five-year survival rate. Furthermore, treatment of surgery combined with radiotherapy demonstrated a better prognosis; however, this association was not statistically significant.

Methylations subgrouping integrated to morphology and survival:

SHH subtype:

By re-evaluating the histomorphology, classified as being SHH pathway in a background of nodular/desmoplastic morphology, the reticulin is rich and clear. All SHH cases, regardless of the morphology, showed negativity for b-catenin, and positivity for synaptophysin. GAB1 shows both cytoplasmic and membranous positivity. The P53 that depicts the aggressiveness in this group, presented as recurrence or survival, is expressed either/or both by immunostaining or by molecular testing as both can co-exist. In the nodular/desmoplastic morphology, the presence of additional anaplasia was seen focally in some cases. Cases presenting with anaplasia, even if focal, did not survive.

WNT subtype:

The age range was from 7 to 14 years old. All cases showed classical morphology with positive nuclear b-catenin stain. Reticulin was negative; however, GAB1 was positive with cytoplasmic staining in all cases. One case proved to be MGMT methylated. For choroidal neovascularisation (CNV) loss, the Myoblastosis (MYB) gene was lost in all cases. This group was free of recurrence and showed progression-free survival.

Group 3 subtype:

The age range was from two to four years old. The morphology was variable. CNV gain was noted in many genes, the most frequent are MET, CCND2, CKD4, MDM4, MYCN, TERT, EGFR, CDK6, and NF1. KIAA1549/BRAF was also noted. CNV loss was noted in FGFR1/TACC1, PTEN, MGMT, CCND1, TP53. Progression was noted in two-thirds of cases.

Group 4 subtype:

This was the largest group, with an age range from 3 to 16 years old. The morphology was also variable between classical and D/N. Both morphological groups were negative for P53 immuno-stain. The D/N can be poor or rich in reticulin. Moreover, PTCH was detected by DNA sequencing in only one case. Anaplasia was noted in one of the cases, in which the patient survived and is free of recurrence. Variable loss of multiple CNVs was noted in different cases, but all were in low frequencies.

Among the 44 cases in our sample, the overall progression-free survival was seen in 27 patients (44%), and the non-specific five-year survival was seen in 31 (71%) after a five-year retrospective follow-up (figure 1).

DISCUSSION

In recent years, several publications have altered the perspective in the approach of pediatric medulloblastomas in terms of the distinctive demographic and radio-genomic features [2, 6-9]. This article aims to identify the potential predictors of a favorable prognosis of this pathology.

Most studies have documented that Medulloblastomas affect males more than females [15, 16, 17]. Around 62% were males and around 38% were females [17]. A study of 55 patients in Saudi Arabia followed the genetic features of a total of 55 patients, and among those 38 patients were males with a percentage of 69.1% [14]. Similarly, we noticed that 70% of our sample were males (Table-1). Curran et al. reported that females have a better survival rate in patients more than three years old [17]. However, in children less than three years old, they reported that females may show less survival advantage [17]. In this study, we did not find any association between gender and the survival rate. The American Brain Tumor Association reported that the median age of diagnosis of pediatric medulloblastoma is seven years old [18]. From our analysis, the median age of diagnosis was 6.5 years. There was no noticeable difference between the specific pediatric age groups and radiological characteristics, molecular features as well as prognosis. The highest survival in the sample was among children between three and nine years of age but without any statistical significance. However, our data did not reflect what the literature states regarding SHH being more common in patients less than three years old, and WNT type more common in patients more than three years old [19, 20].

The radiological characteristics may be affected by the histological and molecular types [21]. Reports indicated that these features could correlate with the medulloblastoma genomic subtype. This can be a strong predictor tool for the subtype for early identification of the subgroup, which can subsequently predict prognosis. However, this has not been definitively decided yet with variations in reports for the MRI features for different groups. In fact, most medulloblastomas arise in the cerebellum, and the majority of those (75%) are midline originating from the vermis [8, 9, 22]. In comparison to pediatric medulloblastomas, it is well-known that adult medulloblastoma tends to locate laterally (9). Likewise, about 70% of our pediatric cases arise from the midline. The location of the tumor is key in predicting the molecular group according to recent literature. For example, midline tumors can predict group 3, group 4, or SHH, while lateral tumors can anticipate WNT, which has a better prognosis [9]. Other MRI features are of less

importance in predicting the genomic pattern [8, 9, 22]. For our results, no association was observed between the location of the tumor and the molecular subgroup (figure 2). Calcification was noticed in 34% of patients, and this was slightly higher than what was reported by Taylor et al (10-20%) [8]. Perreault et al. revealed that around 90% of medulloblastomas enhance with gadolinium contrast [9]. As expected, most of our samples (95%) demonstrated enhancement. Given this finding, we cannot hold a true cause and effect between enhancement and prognosis in our cohort in the Middle East. It is worth mentioning that the lack of association might be affected by the low sample size or due to a different genetic pool of targeted population compared to literature.

Different publications indicated a slight variation in the prevalence of each molecular subtype among pediatric medulloblastoma cases. For instance, a study that summarized four principal publications [23-26] that started the molecular definition demonstrated the prevalence as follows: group 4 (35%), SHH (30%), group 3 (25%), and WNT (10%) [27]. Another multicenter meta-analysis stated that "Group 4 tumors formed the largest group (34%) in this meta-analysis, followed by SHH (28%) and Group 3 tumors (27%), and WNT tumors represented the smallest group (11%)" [23]. Correspondingly, in our single-center sample, the prevalence of all samples in Kuwait in the last ten years was as follows: group 4 (25%), SHH (23%), and WNT (11%). Conversely, group 3 was the least prevalent (7%). Although around 34% were not categorized into a specific molecular group.

Medulloblastoma cases presented in different pathologic morphologic classifications in our cohort, in a decreasing frequency from classical to desmoplastic/nodular to large cell/anaplastic, which is similar to what has been presented in the literature as being classical is the most common [28]. The frequency of medulloblastoma methylation subtyping in our study matches what has been reported regarding group 4 being the most common [29]. Concerning tumor morphologic classification, it did not always represent the molecular group assigned by methylation, as the molecular group can present with different morphological classifications. However, the assistance of immuno-stains such as GAB1, b-catenin, and P53, and histochemical stains, namely reticulin, can predict the molecular group in most cases, with some limitations. Thus, immunostaining is of great help in managing medulloblastoma cases to provide early patient management and prognosis [28]. The presence of focal anaplasia in classical morphologic variants of medulloblastoma was not associated with poor outcome, as it was identified in 17% of cases in which its outcome was comparable to medulloblastoma with classical morphology lacking anaplasia [28-30].

LIMITATIONS & STRENGTHS

First, data collection was retrospective and thus dependent on the records. Another limitation is the slight chance of residual confounding given the nature of the study design.

However, the information was verified and revised to decrease any possibility of bias. An additional limitation was the small sample size despite the long study period. Though, those were all the cases in our facility in the studied duration, which is the only center treating pediatric medulloblastomas in the target population. Furthermore, the multivariable regression model to measure the Kaplan-Meier curve was not applied due to the lack of time-event data in the records. Even so, we were able to determine our primary and secondary endpoints with adjusted probabilities using Pearson's Chi-square test. Lastly, due to this being a long-term follow-up study, not all paraffin blocks were available for analysis and methylation testing.

Despite these limitations, this cohort study is one of the first to thoroughly investigate pediatric medulloblastomas in the Middle East. Since this was a study with a long follow-up, it provides considerable findings in terms of survival rate. Our precise population selection criteria and extended duration created an ideal setting for clean data collection. Our input can contribute to literature on Pediatric Medulloblastomas and hopefully reduce publication bias.

CONCLUSION

To conclude, our findings did not support the association between the majority of the preoperative MRI characteristics and the PFS or the five-year survival rate. However, the enhanced tumors were significantly but questionably correlated with better outcomes. There was also no observed association between the radiographic characteristics, specifically the location of the tumor, and the molecular subgroup. We found that SHH biological type has a better prognosis in comparison with the other types, notably with PFS. In contrast, group 3 had the worst prognosis and survival rate. The crude one-year progression-free survival was seen in 44%, and the five-year survival was seen among 71% of our sample.

Our results deduce that the gross total resection of the tumor, the appropriate adjuvant therapy, and molecular features are the main predictors of the overall survival for Pediatric Medulloblastomas. We yearn to recommend further scrutiny in understanding the natural disease progression and outcome of this disease via a metanalysis involving several hospitals, clinics, and research centers.

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Table 1. Descriptive characteristics of the pediatric patients who underwent treatment for Medulloblastoma in Kuwait (n = 44):

Characteristic	n	%
A- Demographic Characteristics:		
Gender		
Male	31	70.5
Female	13	29.5
Age in years		
< 3	5	11.4
3-9	27	61.4
10-16	12	27.3
B- Radiological Features:		
Location of the tumor		
Midline	31	70.5
Off-midline	13	29.5
Presence of intra-lesional Hemorrhage		
Yes	10	22.7
No	34	77.3
Presence of Calcification		
Yes	15	34.1
No	29	65.9
Enhancement with Gadolinium contrast		
Yes	42	95.5
No	2	4.5
Tumor's consistency		
Solid	5	11.4
Cystic	15	34.1
Mixed pattern	24	54.5
Presence of Hydrocephalus		
Yes	42	95.5
No	2	4.5
Spinal Dissemination		
Yes	10	22.7
No	34	77.3
C- Genetic & Histological features:		
Genetic type		
WNT	5	11.4
SHH	10	22.7
Group 3	3	6.8

Group 4	11	25
Missing/undetermined	15	34.1
MGMT Methylation		
Unmethylated	27	61.4
Methylated	2	4.5
Missing/undetermined	15	34.1
Histopathology		
Classic	12	9.1
Desmoplastic/nodular	17	22.7
Extensive nodularity	1	6.8
Large cell/anaplastic	3	25
NOS	4	9.1
Missing	7	15.9

- % = column %
- WNT: Wingless
- SHH: sonic hedgehog
- MGMT: O[6]-methylguanine-DNA methyltransferase
- NOS: not otherwise specified

Table 2. The association between the following variables and the progression free survival of patients with medulloblastoma after treatment (n= 44):

Item	All (n = 44)	Progression Free Survival		p
		Yes (n = 27)	No (n = 17)	
	n (%)	n (%)	n (%)	
A. Demographic Characteristics:				
Age Categories, in years				0.242
Less than 3	5 (11.4)	4 (14.8)	1 (5.9)	
3-9	27 (61.4)	17 (63)	10 (58.9)	
10-16	12 (27.3)	6 (22.2)	6 (35.2)	
Gender				0.488
Male	31 (70.5)	18 (66.7)	13 (76.4)	
Female	13 (29.5)	9 (33.3)	4 (23.6)	
B. Radiological Features:				
Location of the tumor				0.488
Midline	31 (70.5)	18 (66.7)	13 (76.4)	
Off-midline	13 (29.5)	9 (33.3)	4 (23.6)	
Presence of intra-lesional Hemorrhage				0.585
Yes	34 (77.2)	22 (81.5)	12 (70.6)	
No	10 (22.8)	5 (18.5)	5 (29.4)	
Presence of Calcification				0.089
Yes	29 (65.9)	18 (66.7)	11 (64.7)	
No	15 (34.1)	9 (33.3)	6 (35.3)	
Enhancement with Gadolinium contrast				**0.047**
Yes	42 (95.5)	27 (100)	15 (88.2)	
No	2 (4.5)	0 (0.0)	2 (11.8)	
Tumor's consistency				0.092
Solid	5 (11.3)	3 (11.1)	2 (11.7)	
Cystic	15 (34)	6 (22.2)	9 (52.9)	
Mixed pattern	24 (54.7)	18 (66.7)	6 (35.4)	
Presence of Hydrocephalus				0.073
Yes	42 (95.5)	26 (96.3)	16 (94.1)	
No	2 (4.5)	1 (3.7)	1 (5.9)	

Table 2. Cont.

Item	All (n = 44)	Progression Free Survival		p
		Yes (n = 27)	No (n = 17)	
	n (%)	n (%)	n (%)	
Spinal Dissemination				0.401
Yes	10 (22.7)	5 (18.5)	5 (29.4)	
No	34 (77.3)	22 (81.5)	12 (70.6)	
C. Molecular features:				
Genetic type*				**0.042**
WNT	5 (11.4)	3 (21.4)	2 (13.3)	
SHH	10 (22.7)	7 (50)	3 (20)	
Group 3	3 (6.8)	1 (7.2)	2 (13.3)	
Group 4	11 (25)	3 (21.4)	8 (53.3)	
MGMT Methylation*				0.818
Unmethylated	27 (93.1)	19 (95)	8 (88.9)	
Methylated	2 (6.9)	1 (5.0)	1 (11.1)	
D. Treatment:				
Extent of surgical resection*				**0.019**
GTR	30 (75)	19 (82.6)	11 (64.7)	
NTR	10 (25)	4 (17.4)	6 (35.3)	
Adjuvant therapy				0.078
Only Chemotherapy	9 (21.4)	8 (32)	1 (5.9)	
Only Radiotherapy	1 (2.4)	1 (4)	0 (0.0)	
Combined (chemotherapy & Radiotherapy)	32 (76.2)	16 (64)	16 (94.1)	

- % = column %
- p-values were generated using Pearson's chi-square test.
- Bold type indicates statistically significant P value (P<0.05)
- *Frequencies may not add to the total due to some missing values.
- WNT: Wingless
- SHH: sonic hedgehog
- MGMT: O[6]-methylguanine-DNA methyltransferase
- GTR: gross total resection, NTR: near total resection

Table 3. The association between the following variables and the five-year survival rate of patients with medulloblastoma after treatment (n= 44):

Item	All (n = 44)	Five-year Survival %		p
		Yes (n = 31)	No (n = 13)	
	n (%)	n (%)	n (%)	
A. Demographic Characteristics:				
Age Categories, in years				0.080
Less than 3	5 (11.4)	4 (12.9)	1 (7.6)	
3-9	27 (61.4)	19 (61.3)	8 (61.5)	
10-16	12 (27.3)	8 (25.8)	4 (30.9)	
Gender				0.908
Male	31 (70.5)	22 (71.0)	9 (69.2)	
Female	13 (29.5)	9 (29.0)	4 (30.7)	
B. Radiological Features:				
Location of the tumor				0.054
Midline	31 (70.5)	21 (67.8)	10 (76.9)	
Off-midline	13 (29.5)	10 (32.2)	3 (23.0)	
Presence of intra-lesional Hemorrhage				0.410
Yes	34 (77.2)	25 (80.6)	9 (69.2)	
No	10 (22.8)	6 (19.4)	4 (30.8)	
Presence of Calcification				0.274
Yes	29 (66.0)	22 (71.0)	7 (53.9)	
No	15 (34.0)	9 (29.0)	6 (46.1)	
Enhancement with Gadolinium contrast				**0.050**
Yes	42 (95.5)	30 (96.8)	12 (92.3)	
No	2 (4.5)	1 (3.2)	1 (7.6)	
Tumor's consistency				0.201
Solid	5 (11.4)	2 (6.5)	3 (23.0)	
Cystic	15 (34.1)	10 (32.2)	5 (38.5)	
Mixed pattern	24 (54.5)	19 (61.3)	5 (38.5)	
Presence of Hydrocephalus				0.349
Yes	42 (95.5)	29 (93.5)	13 (100)	
No	2 (4.5)	2 (6.5)	0 (0.0)	

Table 3. Cont.

Item	All (n = 44)	Five-year Survival %		p
		Yes (n = 31)	No (n = 13)	
	n (%)	n (%)	n (%)	
Spinal Dissemination				0.401
Yes	10 (22.7)	6 (19.4)	4 (30.8)	
No	34 (77.3)	25 (80.6)	9 (69.2)	
C. Molecular features:				
Genetic type*				**0.039**
WNT	5 (11.4)	5 (26.3)	0 (0.0)	
SHH	10 (22.7)	8 (42.2)	2 (20)	
Group 3	3 (6.8)	1 (5.2)	2 (20)	
Group 4	11 (25)	5 (26.3)	6 (60)	
MGMT Methylation*				0.573
Unmethylated	27 (93.1)	19 (95)	8 (88.9)	
Methylated	2 (6.9)	1 (5.0)	1 (11.1)	
D. Treatment:				
Extent of surgical resection*				**0.012**
GTR	30 (75)	22 (81.5)	8 (61.5)	
NTR	10 (25)	5 (18.5)	5 (38.5)	
Adjuvant therapy*				0.789
Chemotherapy	9 (21.4)	6 (20.7)	3 (23.1)	
Radiotherapy	1 (2.4)	1 (3.4)	0 (0.0)	
Combined (chemotherapy & Radiotherapy)	32 (76.2)	22 (75.9)	10 (76.9)	

- % = column %
- p-values were generated using Pearson's chi-square test.
- Bold type indicates statistically significant P value (P<0.05)
- Frequencies may not add to the total due to missing values.
- WNT: Wingless
- SHH: sonic hedgehog
- MGMT: O[6]-methylguanine-DNA methyltransferase
- GTR: gross total resection, NTR: near total resection

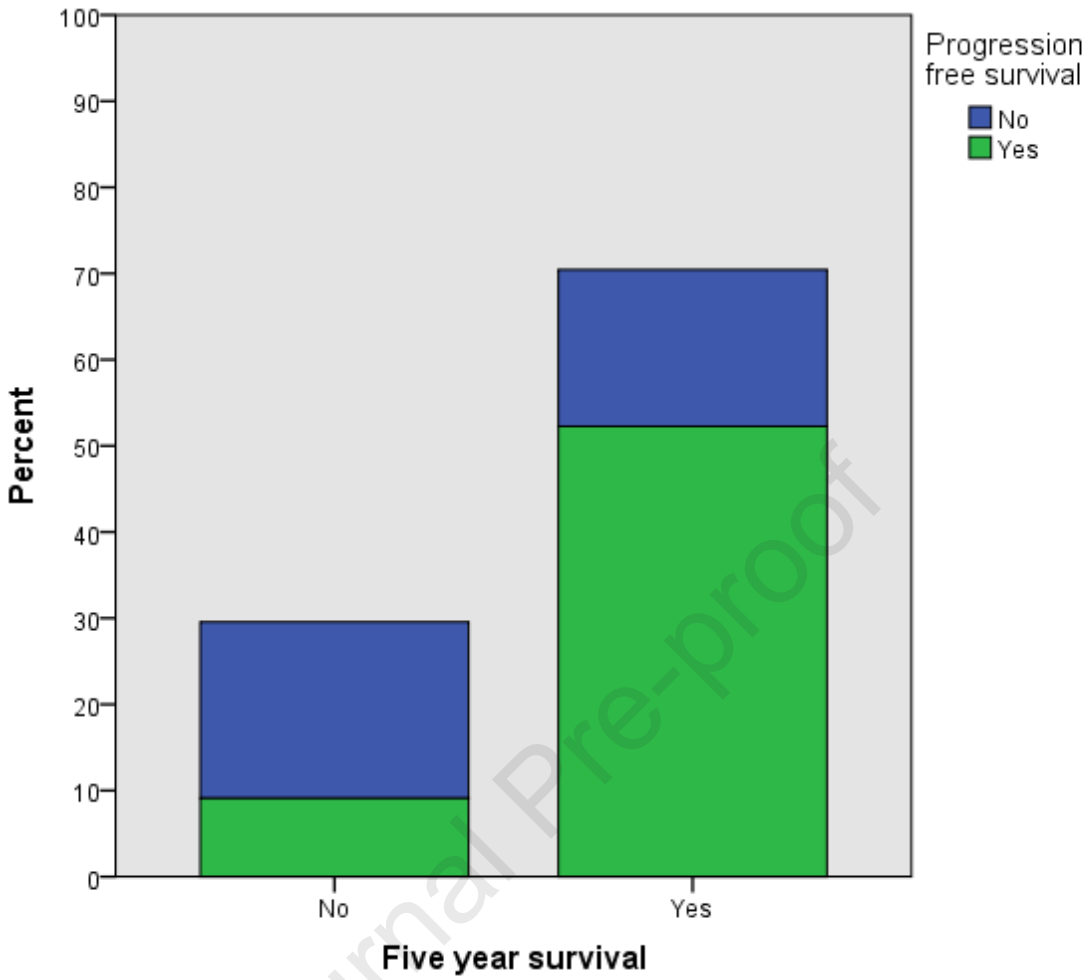

Figure 1. Bar chart of the crude five-year survival rate with illustration of the progression free survival percentage among pediatric patients with medulloblastoma s in Kuwait (n=44).

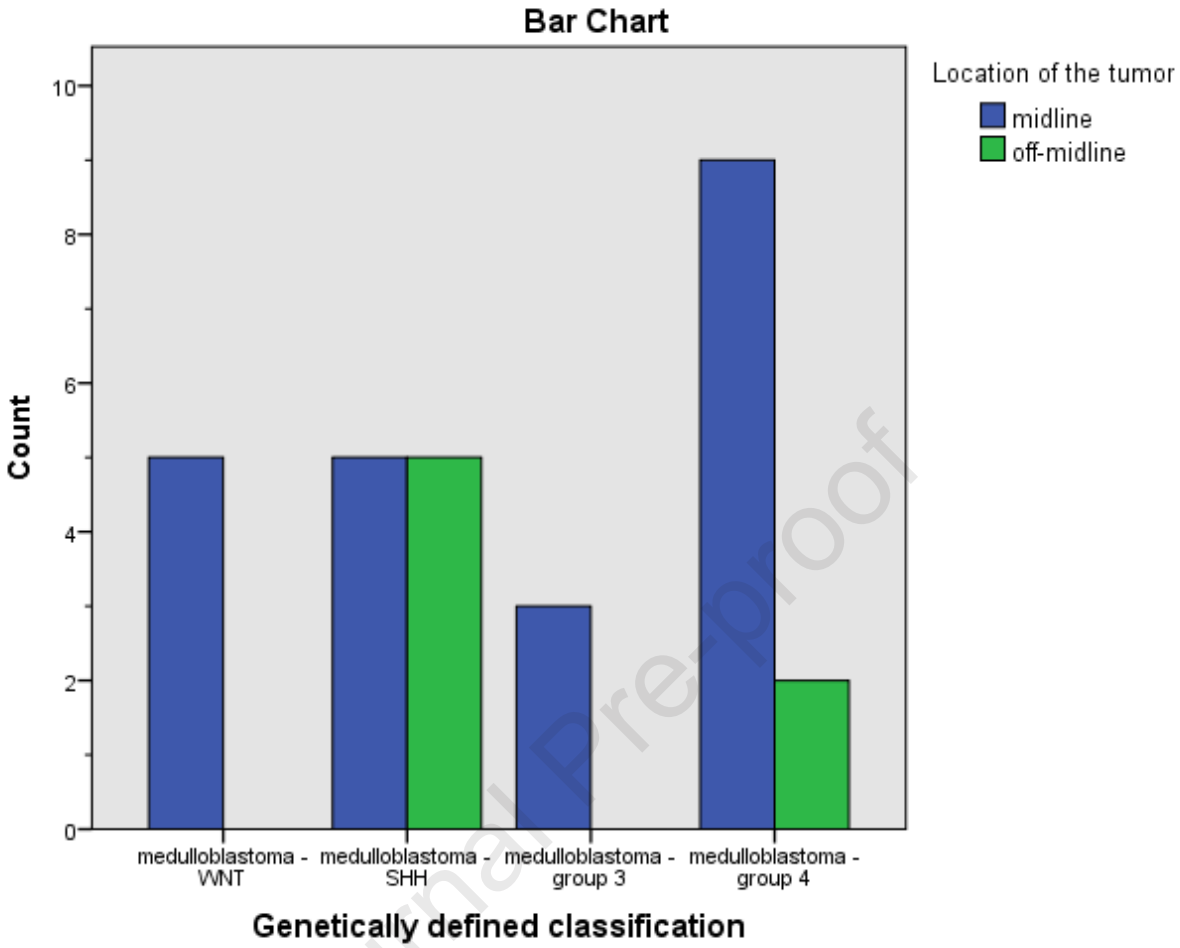

Figure 2. Bar chart demonstrates the location of the tumor according to the genetic molecular type. P=0.093

References

1. Smoll NR, Drummond KJ. The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. J Clin Neurosci. 2012;19(11):1541-1544. doi:10.1016/j.jocn.2012.04.009

2. Waszak SM, Northcott PA, Buchhalter I, et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol. 2018;19(6):785-798. doi:10.1016/S1470-2045(18)30242-0

3. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-820. doi:10.1007/s00401-016-1545-1

4. Crawford JR, MacDonald TJ, Packer RJ. Medulloblastoma in childhood: new biological advances. Lancet Neurol. 2007;6(12):1073-1085. doi:10.1016/S1474-4422(07)70289-2

5. Northcott PA, Korshunov A, Pfister SM, Taylor MD. The clinical implications of medulloblastoma subgroups. Nat Rev Neurol. 2012;8(6):340-351. Published 2012 May 8. doi:10.1038/nrneurol.2012.78

6. Reisinger D, Gojo J, Kasprian G, et al. Predisposition of Wingless Subgroup Medulloblastoma for Primary Tumor Hemorrhage. Neurosurgery. 2020;86(4):478-484. doi:10.1093/neuros/nyz148

7. Schwalbe EC, Lindsey JC, Nakjang S, et al. Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study. Lancet Oncol. 2017;18(7):958-971. doi:10.1016/S1470-2045(17)30243-7

8. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012;123(4):465-472. doi:10.1007/s00401-011-0922-z

9. Perreault S, Ramaswamy V, Achrol AS, et al. MRI surrogates for molecular subgroups of medulloblastoma. AJNR Am J Neuroradiol. 2014;35(7):1263-1269. doi:10.3174/ajnr.A3990

10. Gottardo NG, Gajjar A. Current therapy for medulloblastoma. Curr Treat Options Neurol. 2006;8(4):319-334. doi:10.1007/s11940-006-0022-x

11. Leary SES, Packer RJ, Li Y, et al. Efficacy of Carboplatin and Isotretinoin in Children With High-risk Medulloblastoma: A Randomized Clinical Trial From the Children's Oncology Group. *JAMA Oncol*. 2021;7(9):1313-1321. doi:10.1001/jamaoncol.2021.2224

12. Ramaswamy V, Remke M, Bouffet E, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol*. 2016;131(6):821-831. doi:10.1007/s00401-016-1569-6

13. Amayiri N, Swaidan M, Ibrahimi A, et al. Molecular Subgroup Is the Strongest Predictor of Medulloblastoma Outcome in a Resource-Limited Country. *JCO Glob Oncol*. 2021;7:1442-1453. doi:10.1200/GO.21.00127

14. Al-Harbi M, Mobarak N, Mosleh O, Abedalthagafi M. MEDU-03. MEDULLOBLASTOMA GENOMIC SUBGROUP-SPECIFIC OUTCOMES IN IRRADIATED CHILDREN ABOVE 3 YEARS TREATED AT KING FAHAD MEDICAL CITY (KFMC). *Neuro Oncol*. 2017;19(Suppl 4):iv37-iv38. doi:10.1093/neuonc/nox083.154

15. Millard NE, De Braganca KC. Medulloblastoma [published correction appears in J Child Neurol. 2016 Sep 15;:]. *J Child Neurol*. 2016;31(12):1341-1353. doi:10.1177/0883073815600866

16. Dressler EV, Dolecek TA, Liu M, Villano JL. Demographics, patterns of care, and survival in pediatric medulloblastoma. J Neurooncol. 2017 May;132(3):497-506. doi: 10.1007/s11060-017-2400-5. Epub 2017 Mar 13. PMID: 28290003; PMCID: PMC5481479.

17. Curran EK, Sainani KL, Le GM, Propp JM, Fisher PG. Gender affects survival for medulloblastoma only in older children and adults: a study from the Surveillance Epidemiology and End Results Registry. *Pediatr Blood Cancer*. 2009;52(1):60-64. doi:10.1002/pbc.21832

18. American Brain Tumor Association (ABTA). Medulloblastoma: 2015. https://www.abta.org/wp-content/uploads/2018/03/medulloblastoma-brochure.pdf

19. Dhanyamraju PK, Patel TN, Dovat S. Medulloblastoma: "Onset of the molecular era". *Mol Biol Rep*. 2020;47(12):9931-9937. doi:10.1007/s11033-020-05971-w

20. Ray S, Chaturvedi NK, Bhakat KK, Rizzino A, Mahapatra S. Subgroup-Specific Diagnostic, Prognostic, and Predictive Markers Influencing Pediatric Medulloblastoma Treatment. *Diagnostics (Basel)*. 2021;12(1):61. Published 2021 Dec 28. doi:10.3390/diagnostics12010061

21. Rutkowski S, von Hoff K, Emser A, et al. Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. *J Clin Oncol*. 2010;28(33):4961-4968. doi:10.1200/JCO.2010.30.2299

22. Koeller KK, Rushing EJ. From the archives of the AFIP: medulloblastoma: a comprehensive review with radiologic-pathologic correlation. *Radiographics*. 2003;23(6):1613-1637. doi:10.1148/rg.236035168

23. Thompson MC, Fuller C, Hogg TL, et al. Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. *J Clin Oncol.* 2006;24(12):1924–1931.

24. Kool M, Koster J, Bunt J, et al. Integrated genomics identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features. *PLoS ONE.* 2008;3(8):e3088

25. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. *J Clin Oncol.* 2011;29(11):1408–1414. Principal medulloblastoma subgrouping paper that helped lead to the current consensus four-subgroup classification scheme of the disease

26. Cho YJ, Tsherniak A, Tamayo P, et al. Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. *J Clin Oncol.* 2011;29(11):1424–1430. Significant medulloblastoma subgrouping paper that was first to describe the identity of a poor-prognosis subtype of Group 3 largely driven by *Myc*.

27. Northcott PA, Dubuc AM, Pfister S, Taylor MD. Molecular subgroups of medulloblastoma. *Expert Rev Neurother*. 2012;12(7):871-884. doi:10.1586/ern.12.66

28. Ellison DW, Dalton J, Kocak M, Nicholson SL, Fraga C, Neale G, et. al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol. 2011 Mar;121(3):381-96. doi: 10.1007/s00401-011-0800-8. Epub 2011 Jan 26. PMID: 21267586; PMCID: PMC3519926.

29. Orr BA. Pathology, diagnostics, and classification of medulloblastoma. Brain Pathol. 2020 May;30(3):664-678. doi: 10.1111/bpa.12837. PMID: 32239782; PMCID: PMC7317787.

30. Waszak SM, Northcott PA, Buchhalter I, Robinson GW, Sutter C, Groebner S, et. al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol. 2018 Jun;19(6):785-798. doi: 10.1016/S1470-2045(18)30242-0. Epub 2018 May 9. PMID: 29753700; PMCID: PMC5984248.

Abbreviations:

MRI: Magnetic Resonance Imaging
NOS: Not Otherwise Specified
PFS: Progression-free Survival
SHH: Sonic Hedgehog
WHO: World Health Organization
WNT: Wingless

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