Original Article

Childhood medulloblastoma in Morocco (middle-income country): therapeutic outcomes and survival

Mohamed Jaafari[1], Rachid Razine[2,3], Abbas Ermilo Haroun[2,3], Zakaria Tahiri[1], Laila Hessissen[4]

[1]Doctoral Study Center for Life and Health Sciences, Faculty of Medicine and Pharmacy Rabat, Mohamed V University, Rabat, Morocco; [2]Laboratory of Biostatistics, Clinical and Epidemiological Research, Department of Public Health, Faculty of Medicine and Pharmacy Rabat, Mohamed V University, Rabat, Morocco; [3]Laboratory of Community Health, Department of Public Health, Faculty of Medicine and Pharmacy Rabat, Mohamed V University, Rabat, Morocco; [4]Pediatric Oncology and Hematology Department, Hopital d'enfant Rabat, Faculty of Medicine and Pharmacy Rabat, Mohamed V University, Rabat, Morocco

Contributions: (I) Conception and design: M Jaafari, L Hessissen; (II) Administrative support: None; (III) Provision of study materials or patients: M Jaafari, L Hessissen, Z Tahiri; (IV) Collection and assembly of data: M Jaafari, L Hessissen; (V) Data analysis and interpretation: R Razine, AE Haroun, M Jaafari; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mohamed Jaafari, PhD student. Doctoral Study Center for Life and Health Sciences, Faculty of Medicine and Pharmacy Rabat, Imp. Souissi, Rabat 10100, Morocco. Email: jaafarimohammed15@gmail.com.

Background: Medulloblastoma is one of the most common malignant brain tumors of childhood, the management of medulloblastoma in low and middle-income countries (LMIC) is difficult and there is a lack of epidemiological data and mean features about this childhood pathology in Morocco.

Methods: A retrospective study of 49 medulloblastoma cases diagnosed and treated at the University Hospital IbnSina of Rabat, Morocco between 2010 and 2019.

Results: At the diagnostic moment, the median age was 8 years old [interquartile range: 2, 16], with 27 male and 22 female patients, and the sex ratio was 1.23. The main reason for consultation was raised intracranial tension (headache, nausea, vomiting). Histologically, 22 cases were a classic type, 11 cases were nodular/desmoplastic, and only 2 cases were anaplastic/large cells. The median time from surgery to radiotherapy was 92 days [interquartile range: 31, 336]. Radiotherapy was performed on 42 patients, comprising brain and spinal irradiation with doses of 24 Gy/36 Gy and posterior fossa boost with doses of 18 Gy/54 Gy. All patients received chemotherapy, which involved vincristine, cisplatin, etoposide, cyclophosphamide, and methotrexate. Patients treated with radiotherapy had the best overall survival rates after 5 years, with a mean survival of 87.9 months (P=0.005). Relapsed patients had the worst overall survival rates after 5 years, with a mean survival of 46.5 months, compared to no-relapsed patients (mean survival: 95.2 months, P=0.006). The time from surgery to radiotherapy had a significant statistical P value; we found that patients who started radiotherapy within 120 days had the best overall survival rates (mean survival: 99.4 months) compared to those who started more than 120 days (mean survival: 54.5 months, P=0.017).

Conclusions: The results of this study regarding survival rates were encouraging and close to those found in others series. Finally, this retrospective study provides epidemiological data and the main features of this pathology in Morocco. However, we are still unable to perform a molecular classification, which is important to better understand the pathology and improve the survival rates.

Keywords: Medulloblastoma; childhood; overall survival; treatment

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Introduction

Medulloblastoma is one of the most common malignant brain tumors of childhood, comprising about 20% of all pediatric tumors (1-5). The incidence of medulloblastoma is estimated to be 0.7 per 100,000 children per year, with a male predominance (4). The improvements in the cure and the quality of survival for patients with cancer that have been made over the last three decades are impressive. However, the management of medulloblastoma in low and middle-income countries (LMIC) is difficult due to the expensive diagnostic technology such as computed tomography (CT) and/or magnetic resonance imaging (MRI), complicated neurosurgical techniques, and skilled neurosurgeons, as well as the expensive radiation therapy and lack of radiation centers and skilled radiotherapists. As a result, the therapy outcomes for medulloblastoma in LMIC are characterized by low survival rates and increased mortality. In Morocco, according to the Great Casablanca Register of Cancer, more than 538 cases of brain tumors have been reported in children under 15 years old, with rate of brain tumors accounting for 16% of cases (6). National epidemiological studies of primary brain tumors found that medulloblastoma and pilocytic astrocytoma were the most common types, accounting together for nearly half of the cases (7,8). This study aims to create a clinical profile and describe therapy outcomes and survival rates for patients with this disease. We present this article in accordance with the STROBE reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-22-39/rc).

Highlight box

Key findings

- The study found that the overall survival rates for patients with medulloblastoma in Morocco were low, with a 5-year overall survival rate of 50%.
- The study also found that the delay radiotherapy and the presence of metastasis were significant prognostic factors.

What is known and what is new?

- There is limited information available on childhood medulloblastoma in Morocco.
- The study provides important information on the clinical profile and treatment outcomes of children with medulloblastoma in Morocco. But more research is needed to fully understand.

What is the implication, and what should change now?

- A better understanding of the therapeutic outcomes and survival rates for this disease in Morocco.
- It would be useful to improve the management of childhood medulloblastoma in Morocco and other low and middle-income countries.

Table 1 Risk stratification of medulloblastoma

High risk
Residual tumor >1.5 cm^2
Metastasis disease
Large cell or an anaplastic subtype
≤3 years of age
Standard risk
Residual tumor ≤1.5 cm^2
Classic or desmoplastic subtype
>3 years of age

Methods

Patients and clinical data

In a retrospective approach, we reviewed the medical records of 49 patients with medulloblastoma, diagnosed and treated at the University Hospital Ibn Sina of Rabat between January 2010 and December 2019. Only patients with histological confirmation according to the World Health Organization (WHO) classification 2007 and aged under 18 years at diagnosis were included (9). Clinical data and follow-up were collected from the medical records, including age, gender, the reason for consultation, symptoms, neuroimaging findings, the extent of resection, craniospinal fluid shunting, time from surgery to radiotherapy, duration of radiotherapy, duration of chemotherapy, and treatment results. the postoperative cerebrospinal fluid examination was not routinely performed. The risk stratification was categorized by age, tumor residual size, metastatic disease, and histologic subtype (*Table 1*). The treatment plan included a combination of surgery, radiotherapy, and chemotherapy (*Figure 1*).

Statistical analysis

The qualitative variables were expressed as percentages, while the quantitative variables were presented as means with standard deviations or medians with interquartile ranges. The patients were followed up with routine

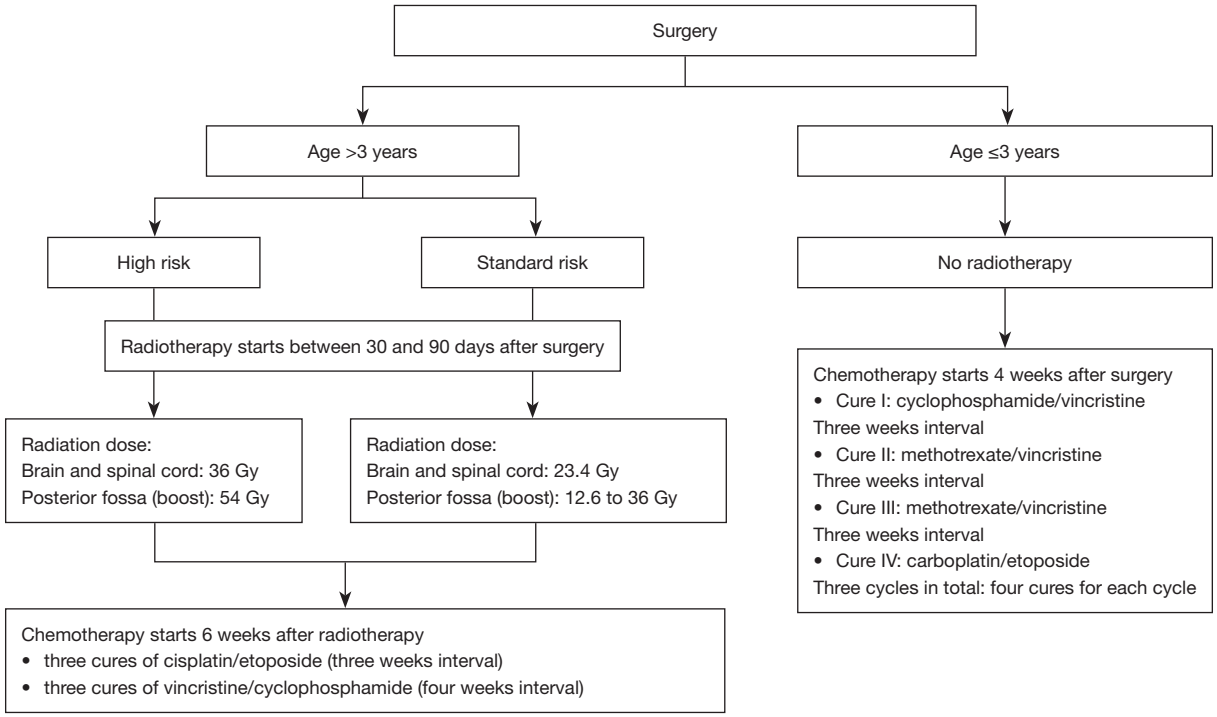

Figure 1 Treatment protocol.

clinical and radiological examinations, and the data were fed into statistical software. Statistical analysis was carried out using SPSS. Overall survival rates were measured from the date of diagnosis to the date of death or last follow-up. Survival curves were constructed using the Kaplan-Meier method, and differences in overall survival between subgroups of patients were analyzed using the log-rank test. A P value ($P \leq 0.05$) was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee for biomedical research (CERB), Faculty of Medicine and Pharmacy Rabat, Mohamed V University/ethics board of AF 69/22, and informed consent was taken from the legal representatives of all the patients.

Results

A total of 82 patients with medulloblastoma were referred to the Paediatric Oncology and Hematology Department of Ibn Sina University Hospital. Of these, 33 were excluded from the study for various reasons: 6 due to lack of histological confirmation, 8 died during treatment, 7 discontinued treatments, 4 were lost to follow-up, 6 had an incomplete medical file, and 2 were transferred to another hospital. The total number of patients recruited with available data was 49 patients (*Figure 2*).

Clinical and radiological characterization

The study included 49 children ranging in age from 2 to 16 years, with a median age of 8 years. Forty-three children were over 3 years old. The study included 27 males and 22 females, constituting a sex ratio (male/female) of 1.23, with a slight male preponderance (55.1% male versus 44.9% female). The most common reason for consultation was raised intracranial tension (headache, vomiting, and nausea), which was reported by 75.5% of patients. Cerebellar symptoms were the second most common, reported by 46.9% of patients. The primary symptoms were headache, nausea, and vomiting, which were reported by 37 patients. Secondly, cerebellar dysfunction symptoms were reported by 23 patients, and vision dysfunction symptoms (diplopia, strabismus, and decreased visual acuity) were reported by

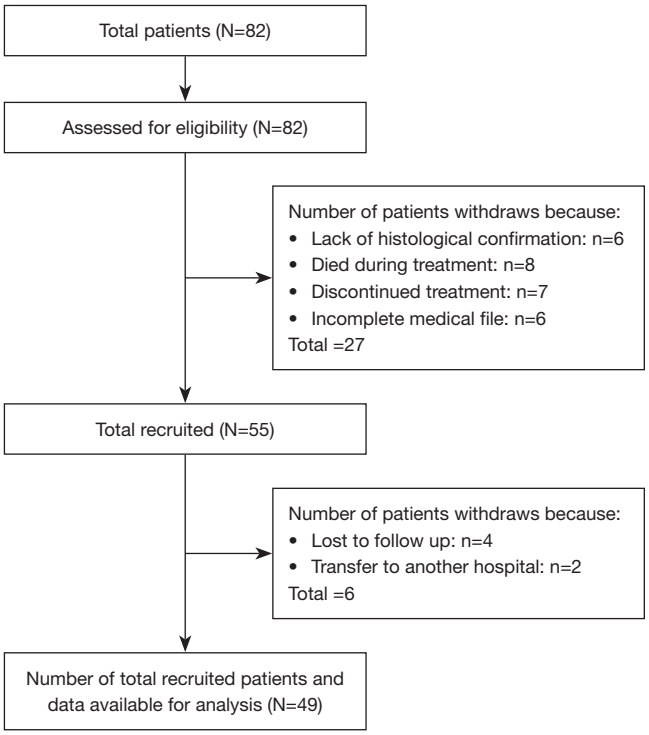

Figure 2 Flow chart diagram.

10 patients. The mean time between the onset of symptoms and consultation was 60 days (range, 30–120 days). Among the medulloblastoma subtypes in our cohort, there were 24 cases of the classic variant, 11 cases of the nodular/desmoplastic variant, and 2 cases of the anaplastic/large cell variant. No cases of the extensive nodular variant were observed. Vermian localization was noted in 40 patients, while hemispheric localization was observed in 8 patients. At the time of diagnosis, there were 9 cases of metastasis, which increased to 37 patients in the post-therapy period. Sixteen patients had tumor residues greater than 1.5 cm². Other results are summarized in *Table 2*.

Treatment and outcome characterization

A total of 37 patients underwent a preoperative ventriculoperitoneal shunt and 9 patients underwent a ventriculocisternostomy. All patients underwent surgery, with complete resection performed in 17 patients, subtotal resection in 21 patients, and biopsy in 11 patients. However, tumor resection was incomplete in 32 patients, 9 of whom had metastasis. A second surgery was necessary for 6 patients due to local relapse. The average time between surgery and radiotherapy was 92 days (ranging from 31–336 days). All patients over 3 years old received radiotherapy, which included spinal and brain treatment with doses ranging from 24 to 36 Gy, as well as posterior fossa irradiation with doses ranging from 18 to 54 Gy. The mean duration of radiotherapy was 45 days (ranging from 36–72 days). All patients received chemotherapy in the postoperative period, which included a combination of vincristine, cisplatin, etoposide, cyclophosphamide, and methotrexate. The average duration was 29 weeks (ranging from 14–39 weeks). Thirty-five patients developed neutropenia during chemotherapy. There were complete responses in 31 patients, a partial response in one patient, stable disease in 6 patients, and progression in 11 patients. Post-therapy neuroimaging was performed on all patients, including 16 cases of relapse and 9 cases of metastasis. The results are summarized in *Table 3*.

Survival analysis

In this study, the median follow-up time was 43.5 months (range 22 to 70 months). The average overall survival of all patients after 5 years was 66 months with a 95% confidence interval (CI): 45.2–86.7. The overall survival rates after 1 year, 2 years, and 5 years were 94%, 84%, and 52%, respectively (*Figure 3*). We observed that the mean duration of overall survival was 72 months in males, while the mean duration in females was 94 months (P=0.19) (*Figure 4*). The 5-year overall survival based on histology was 51.3%, 0%, and 69.7% for classic, anaplastic/large cell, and nodular/desmoplastic types, respectively (P=0.008). The anaplastic type had the worst overall survival rates (*Figure 5*). We found that patients treated with radiotherapy had the best average overall survival (87.9 months) with a statistically significant P value (P=0.005), while others had an average overall survival of 34.5 months (*Figure 6*). The 5-year overall survival rates of complete and incomplete resection were approximately 55% and 51% respectively, with a mean survival of 76 months for complete resection versus 66 months for incomplete resection (P=0.67) (*Figure 7*). By type of risk, high risk patients had the worst 5-year overall survival rates (27.3%) versus 55.5% for standard risk (P=0.021) (*Figure 8*). The time from surgery to radiotherapy had a statistically significant P value if the duration was more than 120 days. We found that patients who started radiotherapy within 120 days had the best overall survival rates (average survival =99.4 months) compared to those who started later than 120 days (average survival =54.5 months)

Table 2 Clinical and paraclinical features (n=49)

Characteristics	Values
Gender	
Male	27 (55.1)
Female	22 (44.9)
Sex-ratio (male/female)	1.23
Age (years)	8.09 [2, 16]
Interval age	
≤3 years	6 (12.2)
>3 years	43 (87.8)
Mean time from the first symptom and consultation (days)	60 [30, 120]
Symptoms	
Nausea and vomiting	37 (75.5)
Headache	37 (75.5)
Cerebellar dysfunction	23 (46.9)
Vision dysfunction (diplopia, strabismus decrease in visual acuity)	10 (20.4)
Facial paralysis	4 (8.2)
Hydrocephalus	
Yes	30 (61.2)
No	19 (38.8)
Tumor location	
Vermis	40 (81.6)
Cerebellar hemisphere	8 (16.3)
No data	1 (2.0)
Tumor residue	
>1.5 cm²	16 (32.7)
≤1.5 cm²	25 (51.0)
No data	8 (16.3)
Metastasis at the moment of diagnostic	
Yes	9 (18.4)
No	40 (81.6)
Histological type	
Classic	24 (49.0)
Nodular/desmoplastic	11 (22.4)
Anaplastic/large cell	2 (4.1)
Not classified	12 (24.5)
Post-therapeutic metastasis	
Yes	37 (75.5)
No	12 (24.5)
Prognosis	
Average risk	22 (44.9)
High risk	27 (55.1)
Neuroimaging post-therapeutic	
Complete remission	29 (59.2)
Tumoral residue	11 (22.4)
Metastasis	9 (18.4)

Data are presented as n (%) or median [interquartile range].

(P=0.017) (*Figure 9*). We also found that patients with metastasis had the worst average survival rates (43 months) compared to patients without metastasis (average survival rates =103.2 months) (P<0.001) (*Figure 10*). The main results are summarized in *Table 4*.

Long-term complications

In our series of 24 surviving patients, 7 patients had no complications. The others suffered from endocrine, neurocognitive dysfunction, neurosensory, and neurological dysfunction. All results are summarized in *Table 5*.

Discussion

Medulloblastoma is a common malignant brain tumor in children, with 80% of cases occurring in children (10). The aim of the study is to describe therapy outcomes and survival rates for patients with medulloblastoma. The median age at diagnosis is 5 to 6 years. The tumor location is principally vermian in childhood (11), and male preponderance was reported with a sex ratio of 1.7 (12). Our results are mostly similar to the results found previously. In our study, we found a small male preponderance, with 55.1% male and 44.9% female, and a sex ratio of 1.23. The median age

Table 3 Treatment and outcome (n=49)

Characteristics	Values
Type of derivation	
Ventriculoperitoneal shunt	37 (75.5)
Ventriculocisternostomy	9 (18.4)
No derivation	3 (6.1)
Surgery	
Yes	49 (100.0)
No	0 (0.0)
Tumoral resection	
Total	17 (34.7)
Subtotal	21 (42.9)
Biopsy	11 (22.4)
The median duration between surgery and radiotherapy (days)	133 [65, 161]
Radiotherapy	
Yes	42 (85.7)
No	7 (14.3)
Spine and brain doses	
36 Gy	33 (67.3)
24 Gy	2 (4.1)
No data	14 (28.6)
Posterior fossa boost	
18 Gy	31 (63.3)
54 Gy	3 (6.1)
No data	15 (30.6)
Mean duration of radiotherapy (days)	45 [36, 72]
Chemotherapy	
Age ≤3 years	6 (12.2)
Age >3 years	43 (87.8)
Agents	
Etoposide	46 (93.9)
Cisplatin	38 (77.6)
Vincristine	41 (83.7)
Methotrexate	5 (10.2)
Endoxan	41 (83.7)
Carboplatin	14 (28.6)
The median duration of chemotherapy (weeks)	20 [18, 32]
Response to chemotherapy	
Complete response	31 (63.3)
Partial response	1 (2.0)
Stable disease	6 (12.2)
Progression	11 (22.4)
Neutropenia	
Yes	35 (71.4)
No	13 (26.5)
No data	1 (2.0)
The mean duration between surgery and chemotherapy (days)	42.4 [12, 67]
Reoperated patients	
Yes	5 (10.2)
No	44 (89.8)
Recurrence rates	
Yes	16 (32.7)
No	33 (67.3)
Type of recurrence	
Local	6 (12.2)
Distant	10 (20.4)

Data are presented as n (%) or median [interquartile range].

at diagnosis was 8 years old, and 46 children were over 3 years old. The most common tumor location was the cerebellar vermis (81.6%), followed by the cerebellar hemisphere (16.3%). These results are consistent with previous Moroccan studies (7,8). Some authors consider age as a prognostic factor, with infants with medulloblastoma generally having poorer outcomes than older children and adults, due to the absence of postoperative radiotherapy and the delayed diagnosis (13,14). In our data, the poor prognosis was noted in patients younger than 3 years, with overall survival rates after 5 years less than 50%. Our data also revealed that the most common clinical manifestation was raised intracranial tension symptoms, such as headache, vomiting, and nausea, in 37 cases. These results are similar

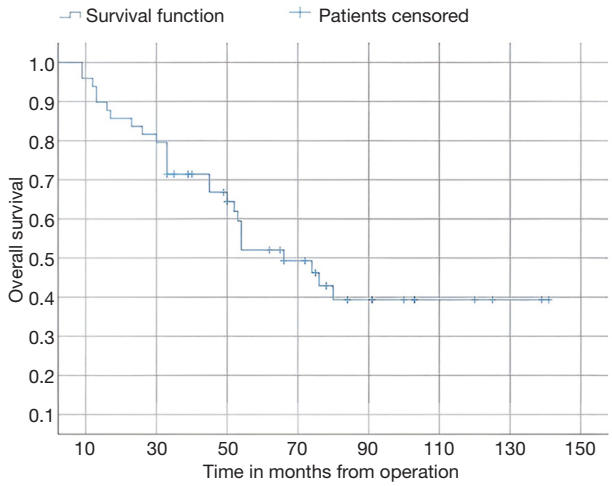

Figure 3 Kaplan-Meier estimates overall survival.

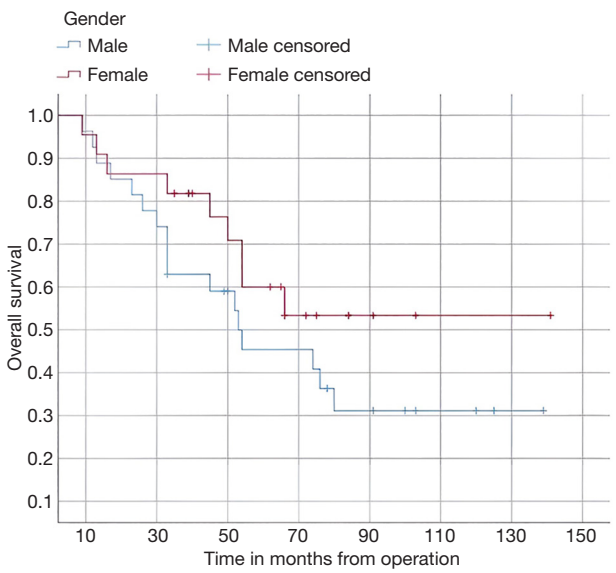

Figure 4 Kaplan-Meier estimates overall survival according to gender.

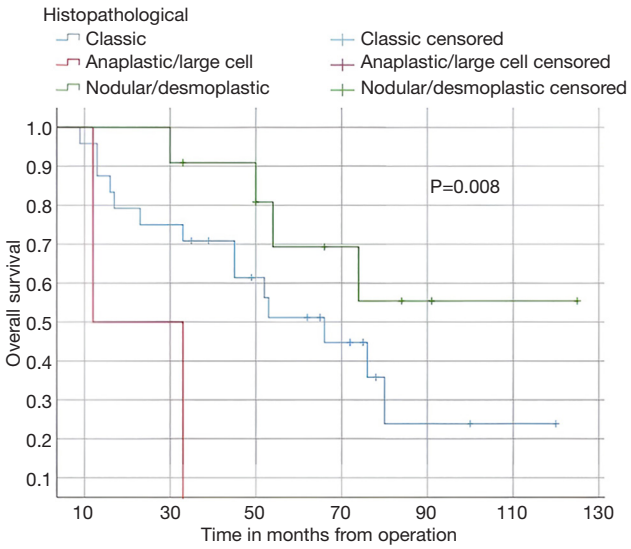

Figure 5 Kaplan-Meier estimates overall survival according to histology type.

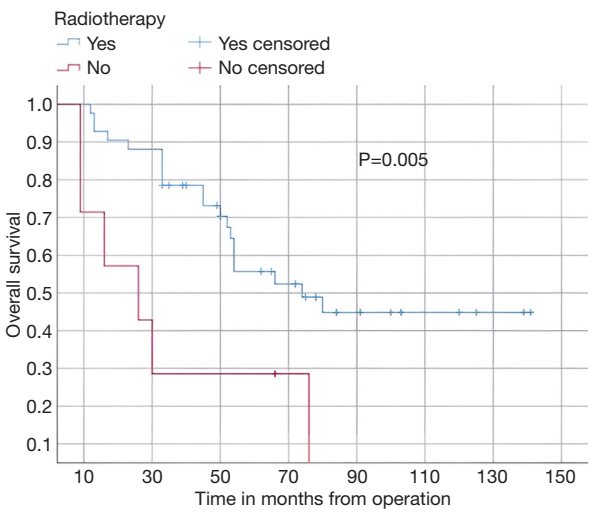

Figure 6 Kaplan-Meier estimates overall survival according to radiotherapy.

to those previously found (15). The role of sex in predicting outcomes of medulloblastoma patients is still controversial, with some studies showing a better prognosis for females (16,17), while others find no influence of gender (18). Our data showed that females had a slight increase in the mean overall survival after 5 years, although this was not statistically significant. The importance of tumor resection was recognized by Harvey Cushing, who noted an increased survival time in patients who underwent total resection compared to biopsy alone (19). On the other hand, gross total resection and near-total resection have not been proven to have similar results (20). In our data, there is no association between overall survival rates and the extent of resection. The interval between surgery and postoperative radiation should not exceed 90 days (16,21). Patients had poorer outcomes with treatment and intervals superior to

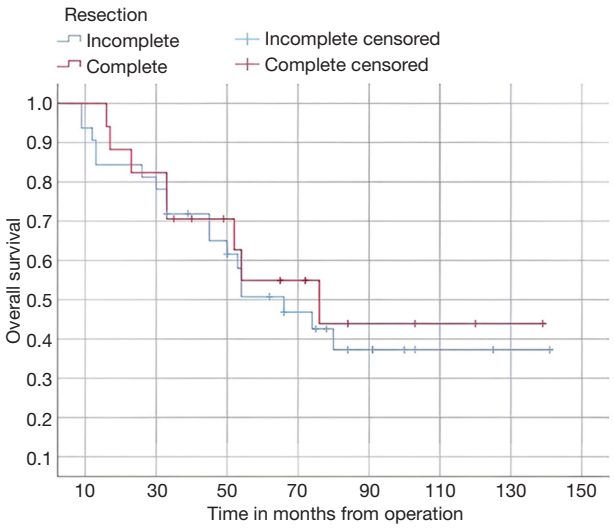

Figure 7 Kaplan-Meier estimates overall survival according to extent of tumor resection.

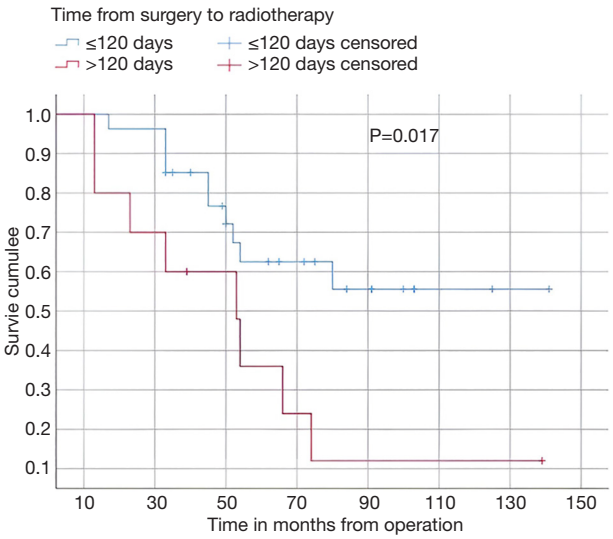

Figure 9 Kaplan-Meier estimates overall survival according to time from surgery to radiotherapy.

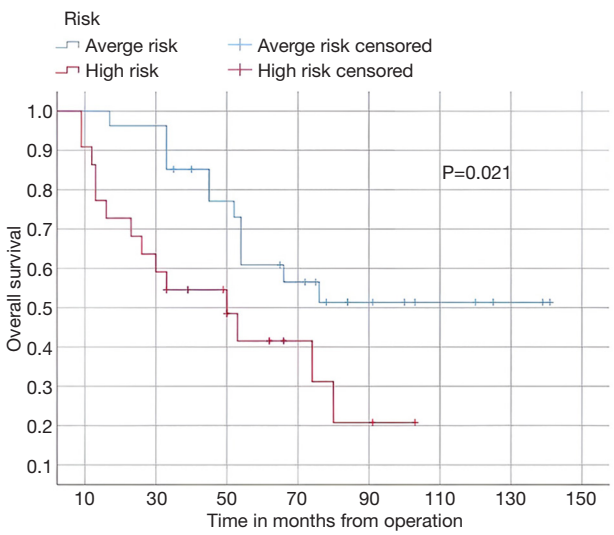

Figure 8 Kaplan-Meier estimates overall survival according to the type of risk.

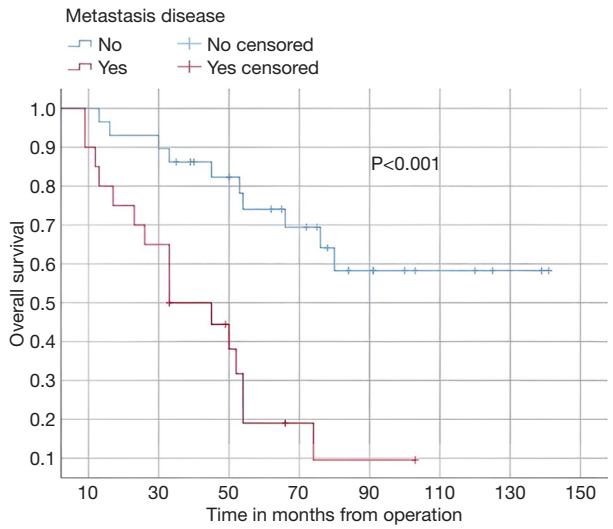

Figure 10 Kaplan-Meier estimates overall survival according to the presence of metastasis.

90 days (18,22). In a randomized trial, time to radiotherapy >49 days showed a trend toward poorer progression-free survival in univariate tests (23). For patients treated with pre-radiation chemotherapy, it is recommended that radiotherapy should commence within 110 days of surgery. The event-free survival was significantly worse for patients starting radiotherapy within 110 days compared to those who started radiotherapy later (P=0.004) (24). In our case, the time from surgery to radiotherapy had a statistically significant value for patients who had radiotherapy within 120 days compared to those who started radiotherapy later than 120 days (P=0.017) overall survival after 5 years was 62% versus 32%. Patients did not undergo timely radiotherapy because the fact that there is only one university radiotherapy

Table 4 Survival according to age, gender, radiotherapy, metastasis, and histology

Characteristics	Overall survival after 1 year, n (%)	Overall survival after 5 years, n (%)	Mean/average [95% CI], months	Log-rank (Mantel_cox), P
Gender				0.19
Male (n=27)	25 (92.6)	10 (37.0)	71.7 [52.37, 91]	
Female (n=22)	21 (95.5)	11 (50.0)	93.9 [70.69, 117.1]	
Interval age				0.5
>3 years (n=43)	40 (93.0)	18 (41.9)	82.7 [66.18, 99.23]	
≤3 years (n=6)	5 (83.3)	3 (50.0)	52 [29.18, 74.82]	
Radiotherapy				0.005
Yes (n=42)	41 (97.6)	19 (45.2)	87.9 [71.5, 104.24]	
No (n=7)	5 (71.4)	2 (28.6)	34.57 [12.4, 56.6]	
Metastasis disease				<0.001
Yes (n=20)	17 (85.0)	3 (15.0)	43.09 [30.4, 55,69]	
No (n=29)	28 (96.6)	17 (58.6)	103.26 [84.7, 121.82]	
Resection				0.67
Complete (n=17)	17 (100.0)	7 (41.2)	76 [40.2, 111.7]	
Incomplete (n=32)	29 (90.6)	14 (43.7)	66 [41.2, 90.7]	
Risk stratification				0.021
Standard risk (n=27)	26 (96.3)	15 (55.5)	95.8 [76.9, 114.6]	
High risk (n=22)	19 (86.4)	6 (27.3)	52 [36.9, 67.7]	
Time from surgery to RT				0.017
≤120 days (n=27)	26 (96.3)	13 (48.1)	99.4 [79.5, 119.3]	
>120 days (n=10)	8 (80.0)	3 (30.0)	54.5 [30.2, 78.7]	

CI, confidence interval; RT, radiotherapy.

Table 5 Long term complication (n=24)

Characteristics	Values, n (%)
No complications	7 (29.2)
Neuro-sensory dysfunction (vertigo, cataract, strabismus, diplopia)	6 (25.0)
Neurocognitive dysfunction (memory disorder, learning difficulty, concentration)	4 (16.7)
Neurological dysfunction (ataxia, facial nerve paralysis)	4 (16.7)
Endocrine (delay puberty, growth hormone insufficiency)	3 (12.5)

center located in the Moroccan capital, which leads to a high flow of patients and postponement of the appointments, as well as several socio-economic issues such as financial and transport difficulties, treatment abandonment, and parents misunderstandings about the disease.

Postoperative radiotherapy was a favorable prognostic factor (P=0.005), and the 5-year overall survival rates were 55%. The seven patients who did not receive radiotherapy in our cohort due to various reasons (age under 3 years, dorsal position difficulties) had worse outcomes with overall survival rates after 5 years at 28%. These results are consistent with the reported data (18,25). Histologically,

the classic type was the most prevalent (n=24), while the desmoplastic/nodular type had the best outcomes with 5 years overall survival rates of 69% (P=0.008). Our results matched those of Rutkowski *et al.* (26). The stage of metastasis influenced 5 years overall survival rates (15%) versus no metastasis (58.6%), P<0.001. The same results were noted in many series (24,27).

Conclusions

The reported results on survival rates were encouraging and close to those found in other studies, finally, this retrospective study provides epidemiological data and the main features of this pathology in Morocco, but we are unable to perform a molecular classification, which is important for a better understanding of the pathology and for providing the best therapeutic advances to patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tro.amegroups.com/article/view/10.21037/tro-22-39/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-22-39/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee for biomedical research (CERB), Faculty of Medicine and Pharmacy Rabat, Mohamed V University/ethics board of AF 69/22, and informed consent was taken from the legal representatives of all the patients.

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