Pediatric and Adult Medulloblastoma: Experience About 96 Cases


National Institute of Oncology, Radiotherapy Department
Corresponding Author: yasmina moukasse
yasminamoukasse@gmail.com

ABSTRACT

Our study is a retrospective analysis of 96 cases of medulloblastoma in children and adults, followed up in the department of radiotherapy of the National Institute of Oncology, over a period of 9 years between January 2002 and December 2010. Medulloblastoma represent, according to literature data, less than 1% of brain tumors in adults, but is the most frequent brain tumor of children. Median age at diagnosis was 8 years for children and 24 years for adults. 63 cases (65.6 %) were males. Symptoms was dominated by intracranial hypertension syndrome occurred in 87 cases (97.8%), associated with a cerebellar syndrome noted in 83 cases (94.3%). The most frequent localization seat in cerebellar vermis in 43 cases (76.8%) for children and in the cerebellar hemisphere in 28 cases (70%) for adults. Diagnosis was based on histological examination of the surgical specimen. Classical histological sub type was predominant 88 patients (91.7% of cases). The first step in the treatment of medulloblastoma is resection of the tumor. Surgical resection was complete in 53 cases (55.2%). Adjuvant radiotherapy associated or not with chemotherapy is essential. Irradiation of the entire central nervous system at the dose of 36 Gy, followed posterior fossa boost to 56 Gy was performed in 74 cases (77.1 %). The 5 year overall survival rate for the whole patients was 50%. Therapeutics advances, especially in radiation therapy techniques, improve the efficiency of the treatment, increasing survival and reducing sequelae.

Keywords: Medulloblastoma, Child, Adult, Radiation therapy, chemotherapy

1. INTRODUCTION

Medulloblastoma is a malignant central nervous system embryonal tumor common in the pediatric population (30% of brain tumors) and rare in adults (3% of all primary brain tumors) [1]. Median age at diagnosis is 5 years [2]. Standard of treatment is multidisciplinary including surgery, adjuvant radiation therapy and chemotherapy. The overall survival at five years is about 80% whatever the stage [1,3].

The aim of the present study was to discuss the different aspects of medulloblastoma by highlighting the importance of multidisciplinary management, therapeutic advances and their future implications.
2. METHODS

Our study is a retrospective analysis of 96 patients (children and adults) with medulloblastoma, followed up in the department of radiotherapy of the National Institute of Oncology, over a period of 9 years between January 2002 and December 2010. Statistical analysis was performed using IBM SPSS statistics software.

3. RESULTS

In the study, there were 56 children (58.3% of cases) (<15 years) and 40 adults (41.7% of cases) (≥15 years). The median age of the pediatric population was 8 years [5 - 10] and for adult it was 24 years [21.25 – 31.75]. There were 63 male (65.6 % of cases) and 33 females (34.4 % of cases) with a sex ratio of 1.9 (Table 1).

Table 1: Gender distribution of medulloblastoma

<table>
<thead>
<tr>
<th>Gender</th>
<th>Adults (n = 40)</th>
<th>Children (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>

Duration of symptoms varied from 1 to 3 months. They were dominated by intracranial hypertension syndrome occurred in 87 patients (97.8% of cases), associated with a cerebellar syndrome noted in 83 patients (94.3% of cases) (Table 2).

Table 2: Symptoms of medulloblastoma

<table>
<thead>
<tr>
<th>Variant</th>
<th>Adults (n = 40)</th>
<th>Children (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension syndrome</td>
<td>37 (94.9%)</td>
<td>50 (89.3%)</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>38 (95%)*</td>
<td>45 (93.8)*</td>
</tr>
<tr>
<td>Vestibular syndrome</td>
<td>8 (20.5%)*</td>
<td>8 (17%)*</td>
</tr>
</tbody>
</table>

*missing data

Preoperative brain MRI and/or CT scan were performed in all of our patients. For children, the most frequent localization seat in the cerebellar vermis in 43 patients (76.8% of cases) and for adults, the tumor was mostly located in the cerebellar hemisphere (28 patients (70% of cases)). Diagnosis is based on histological examination of the surgical specimen. Classical histological subtype was predominant in 88 patients (91.7% of cases) (Table 3).

Table 3: Histopathological variants of medulloblastoma

<table>
<thead>
<tr>
<th>Variant</th>
<th>Adults (n = 40)</th>
<th>Children (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>Desmoplastic</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

The treatment was based on surgery in all cases. 66 of cases (68.8%) had a preoperative ventriculoperitoneal shunt. Surgical resection was complete in 53 patients (55.2% of cases) and incomplete in 43 patients (44.8% of cases) (Table 4).

Table 4: Extent of resection of medulloblastoma

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Adults (n = 40)</th>
<th>Children (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Subtotal</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Partial</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Biopsy</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Residual tumor on the immediate postoperative imaging was found in 37 cases (51.4% of cases). Irradiation of the entire central nervous system was performed in 74 patients (77.1 % of cases). 43 patients (58% of cases) was treated with Cobalt machine (2D simulation); and all of our patients how were treated with 3D conformal therapy (31 patients (42% of cases)), were positioned prone using a full-body immobilization device, forehead and chin rest, and the mask for head immobilization. Target volumes were delineated on every slice of the planning CT following the internationals guidelines of delineation. 36 Gy in 20 fractions was given for the whole cranio-spinal axis, and boost to 54Gy for the posterior fossa. Lateral opposed fields were used to treat the brain and a one (or two) directs anterior field was used to cover the spinal axis. The field junction over the cervical cord was moved daily. 21 patients (33.9% of cases) received postoperative chemotherapy; Etoposid-Cisplatin was the most used protocol.

Sites of progression were local recurrence alone in the posterior fossa (17 patients), dissemination to the spinal axis (13 patients) and diffuse bone metastases (3 patients). The median time to recurrence was 14 months.

A mean follow-up of 100 months was noted. The 5-year overall survival rate for the whole patients was
50%. For children, it was 50% and 38% for adults. (Fig. 1, 2 and 3).

Fig.1: Overall survival for children and adults patients

Fig.2: Overall survival for children

Fig.3: Overall survival for adults

4. DISCUSSION

Medulloblastoma is a malignant central nervous system embryonal tumor common in the pediatric population representing about 30% of brain tumors; and uncommon in adults (3% of all primary brain tumors) [1]. The mean age at diagnosis is 5 years for children [2] and 24 years for adults [4], same median ages was found in our series for adults, and for children it was 8 years. Most frequent symptoms that we reported are intracranial hypertension syndrome and cerebellar syndrome, as in other reported series. We also found that were distributed equally in both the populations [5,6]. Neuroradiological imaging of the tumor is based on preoperative contrast-enhanced brain MRI: Technique of choice to specify the situation of the tumor (most often vermian for children and hemispherical for adults), its dimensions, the infiltration at the fourth ventricle, brainstem and cerebellar peduncles; and to explore the supratentorial floor. Immediate postoperative MRI should be done at least 48 hours of surgery (expert recommendations) [7]. In addition, MRI of the spine and cerebrospinal fluid cytology from a lumbar tap are part of staging. Because of high rate of patients who present obstructive hydrocephalus at diagnosis, preoperative ventriculoperitoneal shunt has always to be discus. There is no consensus on the optimum management. Part of the patients can be treated with corticosteroids waiting for the surgery and the cerebrospinal fluid flow can be restored by the tumor resection itself [8]. In our series, 66 of cases (68.8%) had a preoperative
ventriculoperitoneal shunt. Pre-resectional endoscopic third ventriculostomy has been suggested as an efficient alternative measure [9]. The principles of the surgery are a maximum resection of the primary tumor with minimal neurological damage. In different series, complete resection can be possible in 80% of cases [10], in our study; we have 55% of complete resection for both groups. Few cases of 5-aminolevulinic acid (5-ALA) fluorescence assisted-surgery in pediatric medulloblastoma was reported [11], concluding that this technique is not particularly useful to guide resection [12]. Complications of tumor surgery include bleeding, infection, acute hydrocephalus and posterior fossa syndrome (mutism, ataxia, and emotional instability) [13].

Histopathological examination of the operative specimen allows the diagnosis of medulloblastoma. World Health Organization 2016 (WHO) [14] classified medulloblastoma genetically and histologically in group of embryonal tumors (removing the term primitive neuroectodermal tumor or PNET). Histological subtypes are the classical medulloblastoma, desmoplasic/nodular medulloblastoma, medulloblastoma with extensive nodularity and large cell/anaplastic medulloblastoma. Medulloblastomas genetically (molecularly) defined are divided into four groups: Medulloblastoma WNT-activated, medulloblastoma SHH-activated (Sonic hedgehog) and TP53-mutant, medulloblastoma SHH-activated and TP53-wildtype, medulloblastoma non-WNT/non-SHH group3 (tending to harbor MYC amplification) and group 4 (tending to have isochromosome 17q).

Initially, TM staging system known as Chang classification was used, based on intraoperative staging system (determination of the size and location of the tumor by the surgeon at the time of operation and impressions of the extent of dissemination) [15]. Actually, staging is based on pre- and postoperative neuroimaging on two groups: Standard risk for recurrence (No evidence of metastasis (brain, spine, cerebrospinal fluid, extraneural), small-volume residual disease (contrast volume < 1.5 cm²) and classic or desmoplasic histology) and high risk for recurrence (Unresectable tumor or residual tumor > 1.5 cm² or disseminated disease within or outside of the neuroaxis or large cell/anaplastic medulloblastoma or supratentorial location) [16].

The postoperative standard of care of medulloblastoma is craniospinale irradiation [17]. Techniques of irradiations are 3D conformal therapy, intensity-modulated radiotherapy (IMRT) with advantages to deliver a homogeneous dose to the clinical target volume (CTV) with the lowest possible dose to organs at risks [18]. Imageguided adaptive radiotherapy (IGART) can reduce the planning target volume (PTV) [19], and proton beam therapy (PBT) reducing long-term toxicities and risk of second cancer (particularly for pediatric patients) [20]. This high-techniques of irradiation needs a very high-precision on CTV delineations following the most recent SIOPE guidelines [21]. The current recommendations for dose to standard-risk disease are 30-36 Gy to the craniospinal axis [22] (reduced dose 23.4 Gy may consider with adjuvant chemotherapy (protocol of Children's Oncology Group COG) [17, 22]) and boosting the primary brain site to 54-55.8Gy. While for high-risk disease is 36 Gy and boosting the primary brain site to 54-55.8Gy with adjuvant chemotherapy. Children <3 years of age are at high risk of severe neurologic impairment if their initial treatment includes craniospinal radiation therapy, follow protocols that use combination chemotherapy and irradiation.

Weekly Vincristine protocol during craniospinal radiation therapy followed by Cisplat, Cyclophosphamide and Vincristine [17] or Cisplatin, Lomustine and Vincristine [23] is recommended on adjuvant chemotherapy. 20-30% of patients will relapse after their treatment [24]. Relapses are local in a one-third of patients, disseminated (brain or spine) in one-third, and both local and disseminated in the remaining third [17, 25]. In our series, we count 33 patients (34.38%) who relapse.

The follow up of patients after treatment needed performing a history and physical examination every 3 months for the first 1-2 years, then every 6-12 months thereafter, and obtaining brain and spine MRI to monitor for recurrence.

Factors that are associated with worse prognosis include young age, disseminated or metastatic disease at time of diagnosis, residual disease after resection, large cell and anaplastic histology, and MYC amplification [26].

75% of children with medulloblastoma will survive into adulthood. Children younger than 3 years have a poor prognosis with a 5 years overall survival of 40-50% [27]. Young children with disseminated at the time of diagnosis have also poor prognostic with a 5 years overall survival of 15-30% [27]. In the most studies, adults have a worse prognosis compared with children [28]. We found same results in our series (The
5-year overall survival rate 50% was for children and 38% for adults.
Surgery, radiation therapy and chemotherapy can cause complications and repercussion on quality of life in patients who survives [29]. They can present neurocognitive impairment, hearing loss, short stature, endocrine abnormalities, cataracts, cerebrovascular disease and secondary cancers, spacially for pediatric population [26]. Therapeutics advances, especially in radiation therapy techniques, improve the efficiency of the treatment, increasing survival and reducing sequelae.

REFERENCES

COMPETING INTERESTS
The authors have declared that no competing interest exists.

ETHICAL APPROVAL
Ethics Committee of the National institute of Oncology, Mohammed 5 University, Rabat, Morocco

ACKNOWLEDGEMENTS
We thank neurosurgery department, oncologic and pediatric department, radiation therapy department and our colleagues at National institute of Oncology of Rabat who provided care and support for this patient.


