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Posterior fossa ependymomas in children: still a challenge for pediatric neurosurgeons and oncologists.

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Abstract

Introduction: Posterior fossa ependymomas in children are associated with a poor prognosis. This retrospective study tries to determine prognostic factors for the outcomes and the quality of life. Material and Methods: Thirty-three patients with posterior fossa ependymomas were treated from 2002 to 2018. All patients had a cranio-spinal MRI and 3.12% were metastatic. Removal was complete in 29 patients (90.62%). All patients received a complementary treatment: 11patients chemotherapy, radiotherapy in 35 patients, 24 cases of neoadjuvant type and for recurrence in 11. Results: Average age was 5.8 years with a range from 9 months to 18 years. The sex ratio was 2.3 (M/F: 23/10). Sixteen patients had one recurrence (3 metastatic). 90% of the EpPCF were of the PFA group. Overall Survival was 65% with a mean follow-up of 8.4 and a median of 9 years. Twenty-one patients were alive (63.63%) at last follow-up. All were tumour-free according the MRI except 2 patients, 1 with a stable residue for 5 years and 1 in palliative treatment for metastatic recurrence for 5 years. Post-operative complications were as follow, facial nerve palsy in four cases (12.12%), swallowing disorders in three cases (9.09%), transient cerebellar syndrome in 4 cases (12.12%). Fifteen patients had normal schooling. Conclusion: Posterior fossa ependymomas are aggressive tumors. Complete surgical removal remains the most important prognostic factor even if responsible of sequels. Despite molecular studies and the expression of different genes, no obvious therapeutic target has yet emerged.

Posterior fossa ependymomas in children:

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Abbreviations:

EpPCF	Posterior fossa ependymoma
OS	Overall Survival
ETV	Endoscopic Third Ventriculocisternostomy
SFOP	Société Française d'Oncologie Pédiatrique
VABS	Vineland Adaptive Behaviour Scales
PFS	Progression Free Survival
MRI	Magnetic Resonance Imaging
CSF	CerebroSpinal fFuid
WHO	World Health Organization
CPA	CerebelloPontine Angle

Questions and data availability

Question about the study and the data that support the findings of this study are available from the senior author (Carmine Mottolese) upon reasonable request.

ABSTRACT

Introduction: Posterior fossa ependymomas in children are associated with a poor prognosis. This retrospective study tries to determine prognostic factors for the outcomes and the quality of life.

Material and Methods : Thirty-three patients with posterior fossa ependymomas were treated from 2002 to 2018. All patients had a cranio-spinal MRI and 3.12% were metastatic. Removal was complete in 29 patients (90.62%). All patients received a complementary treatment: 11patients chemotherapy, radiotherapy in 35 patients, 24 cases of neoadjuvant type and for recurrence in 11.

Results : Average age was 5.8 years with a range from 9 months to 18 years. The sex ratio was 2.3 (M/F: 23/10). Sixteen patients had one recurrence (3 metastatic). 90% of the EpPCF were of the PFA group. Overall Survival was 65% with a mean follow-up of 8.4 and a median of 9 years. Twenty-one patients were alive (63.63%) at last follow-up. All were tumour-free according the MRI except 2 patients, 1 with a stable residue for 5 years and 1 in palliative treatment for metastatic recurrence for 5 years. Post-operative

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complications were as follow, facial nerve palsy in four cases (12.12%), swallowing disorders in three cases (9.09%), transient cerebellar syndrome in 4 cases (12.12%). Fifteen patients had normal schooling.

Conclusion : Posterior fossa ependymomas are aggressive tumors. Complete surgical removal remains the most important prognostic factor even if responsible of sequels. Despite molecular studies and the expression of different genes, no obvious therapeutic target has yet emerged.

Introduction :

Posterior fossa ependymoma (EpPCF) in children have a different behavior from other localizations [1, 2] and differ from adult EpPCF [3, 4]. A complete removal combined with craniospinal irradiation +/- chemotherapy is the treatment of choice [5, 6]. However, despite new therapeutic strategies, their management remains a challenge with a high rate of recurrence, mortality and a limited overall survival. We reviewed our patients treated from 2002 to 2018 for a posterior fossa ependymoma to report their evolution after surgery and new therapeutic strategies adopted in recent years.

Material and Methods:

Forty-nine children operated for a central nervous system ependymoma between 2002 and 2018: 33 were located in the cerebral posterior fossa. Among these patients, seven were recurrences (five patients were operated on in another center for the first surgery). The mean time for diagnosis was 1 month. The clinical picture was dominated by an aspecific intracranial hypertension in 18 patients (54.5%), a torticollis in six patients (18.18%) and cerebellar troubles in four patients (12.1%). All children had a cranio-spinal MRI scan before removal of the tumor. All patients had a anatomopathological study of cerebrospinal fluid (CSF) after an endoscopic third ventriculocisternostomy (ETV) for 42.4% of cases or by a lumbar puncture at 15 days after surgery for the remaining 57.6%. Fourteen patients (42.4%) had an ETV before surgery. The mean time between VCS and surgery was 3 days. Surgery was performed in sitting position in 32 patients and in prone position in 1 patient for an in interventricular cardiac shunt defect. The removal was assessed by a post-operative MRI performed within 24/48 hours (Figure 1). A residue was reported in seven patients on the post-operative MRI (78.12% total resection) while the resection has been judged macroscopically complete in all but three by the surgeon. In five patients the complete resection was obtained after a second-look surgery before further treatments. Sixty-five surgeries were performed for 33 patients (33 initial + 32 for recurrence). Two patients were operated on for a spinal metastasis. All patients had a complementary treatment: chemotherapy alone for children younger than 3 years of age and/or combined with local radiotherapy even for infants. Eleven patients received postoperative chemotherapy (6 neoadjuvant and 5 relapse) and 35 radiotherapy (24 neoadjuvant and 11 cases at relapse) including neoadjuvant proton therapy (4 neoadjuvant cases and 2 at the relapse). The dose varied from 54 to 59.4 Gy according the SFOP protocols. Concerning chemotherapy: 2 protocols were used the "BB-SFOP" with 3 cycles alternating every 21 days with 7 cycles in total and the SIOP EPENDYMOMA II.

All patients, except one who died in the 1st year of surgery, benefited during the follow-up of a cerebrospinal MRI every 3 months in the first year, every 6 months for two consecutive years and every year until the fifth year. Endocrine sequels after radiotherapy were observed in 3 patients (9.09%). A neuropsychological assessment was performed in all children at 1 and 3 years of surgery by a pediatric neuropsychologist with an age-appropriate IQ evaluation and the Vineland Adaptive Behaviour Scales (VABS). Quality of life was analyzed in all 21 alive patients. Survival curves (OS), were calculated according to Kaplan-Meier curves for overall survival, 5-year survival, progression-free survival (PFS). Differences with a $p < 0.05$ were considered statistically significant. Quality of life and overall motor function were scored with the Barthel Index and the Euro Qol 5 Dimensions (EQ-5D) scale. Educational outcomes were classified as normal and assisted schooling or specialized institution. No patient was lost to follow-up. The study was accepted by the local ethical committee

Results :

The mean age at diagnosis was 5.8 years old (median 4.7 years old, range: 9 months to 18 years). The most

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represented age range was between 3 and 6 years old with 12 cases (36.4%). There was a predominance of males, with 23 males for 10 females. The lesions were located in the fourth ventricle in 28 patients (84.8%), in the cerebellum and the cerebellopontine angle in 3 (9.1%) and 2 cases (6.1%) respectively. At the time of diagnosis, tumor cells were found in one patient's CSF. Twenty patients had a Grade II and 13 had a Grade III, and we noted a Grade II to Grade III mutation at recurrence in 2 patients. The majority of the EpPCF were of the PFA group (90%). The main complications in the early postoperative period were cranial nerve palsy in 14 patients. A patient could have several nerves affected at the same time; facial nerve damage in 4 patients, abducens nerve damage in 5 cases, and oculomotor nerve damage in 2 patients. Six had mixed nerve damage, 2 of which required tracheotomies. A cerebellar mutism was observed in 2 patients. The overall survival rate of our series was of 63,6% and the mortality was of 36,3 % (n=12). The median survival was of 122 months and the median was of 104,7 months. The 10-year survival was 42,4 % (n=14) and the five years' survival was of 63,6 % (n=21). The progression-free survival rate at 5 years was 57.69%. Male's and female's OS (65.2% and 66.7% respectively) did not differ significantly($p > 0.05$) (Figure 2). OS was of 73.7% and 53.8% for WHO grade II and III ($p > 0.05$) (Figure 3). Sixteen patients (48%) had a recurrence (10 patients Grade II and 6 patients Grade III). Eight were children (47%) aged 0 to 3 years. Six patients (20%) were submitted to a second-look surgery to obtain a complete removal that was possible in four patients after the control MRI. In two patients, histology revealed an inflammatory granuloma. One patient refused surgery after a first recurrence and 2 others after a 4th recurrence. The metastasis rate after the initial surgery was 18.2% (6 patients) (Figure 4).

Twelve patients died: 10 for a progression (despite an initial complete removal) after relapse surgery and additional treatment. One patient died after a recurrence and the family refused a new operation and another after post-operative bulbar respiratory complications.

Morbidity was represented by: facial nerve palsy in 4 cases and swallowing troubles in 3 cases. Four patients had transient cerebellar syndrome. Five patients needed a ventriculo-peritonea shunt. Fifteen patients had a normal school program; six patients have had special schooling (Auxiliary for School Life). All had been assessed by the Service Mobile d'Accompagnement d'Evaluation and de Coordination (SMAEC). Among the 9 adult patients, 6 completed their studies and 3 are still students. Eight adults have normal full-time employment. We could identify 3 groups of patients: patients with a complete removal and alive (18 patients), patients with a complete removal and dead (8 patients) and patients with an incomplete removal (7 patients).

In the first group, four patients presented a recurrence (in the cerebello-pontine angle one case, two in the midline, at level of the floor of the fourth ventricle one case. All 18 patients are alive with a mean survival of 12 years (range: 6 to 19 years).

In the second group, one patient presented an extension at level of the floor of the fourth ventricle, three patients an extension in the cerebello-pontine angle of the left side and two of the right side and one in the cerebellar hemisphere.

All received a complementary treatment: only radiotherapy (5 cases), chemotherapy associated with radiotherapy (two cases) and only chemotherapy (one patient aged two years old).

Five patients presented an ependymoma of grade III with PFA signature in 3. All patients presented a recurrence and all were operated with a new complete removal and the survival varied from two months to 109 months with a median survival of three years and one months.

In the third group, only two patients are alive and 5 died. In this group, four patients had radiotherapy and three were treated with a radiotherapy associated with chemotherapy.

Two patients were operated three times and one patient was operated five times.

In this group, patient who presented a recurrence died after four years, twenty-two years, one year and two years.

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Five patients were treated with radiotherapy and two patients with chemotherapy.

Discussion:

Ependymoma is the third most common tumor in the posterior fossa in children [7, 8]. They account for 20-30% of central nervous system tumors [2, 9, 10]. In our series, EpPCF account for 78.6% of intracranial ependymomas [7, 11, 12].

The average age was 5.8 years old as in the literature [13, 14], some authors reported an average age of 3 to 4 years [6, 15]. If it is known a predominance in infancy [16], our series confirm a higher frequency in childhood with 36.4% [17]. A peak between 4 years old and 6 years old has been observed[2]. The male predominance in our series is classic and reported by many authors [6, 7, 15]. Diagnosis time is short and a British study reported an average delay of 3 months[18]. The clinical picture is dominated by an aspecific intracranial hypertension.

Ependymomas are classified according the World Health Organization (WHO) as grade II and III [2]. This classification was not correlated to the prognosis. In recent years, the significant advance has been the differentiation of the PFA and PFB groups that can be determined by the use of anti-H3K27me immunohistochemistry [12]. Their classification therefore depends on the genetics of the tumors and their location. Pajtler reported nine new subgroup without a clinical and therapeutical improvement [19].The PFA form remains predominant with a poor prognosis compared to the other group[3, 20]. Tanrıkulu stated that there was no significant difference between PFA and PFB in terms of resection, disease recurrence and the prognosis of the molecular subgroup based on H3K27me3 status[6] . Tumor harboring 1q+ gain in PFA group had an inferior PFS showing the importance of molecular grouping [21]. Bayliss et al [22] reported that these tumors did not have recurrent gene A MRI scan performed within the first 48 hours is necessary to confirm a complete resection because after this time it is difficult to differentiate between a hematoma or a tumor residue. The 12% progression rate in patients without tumor residue few months after a complete surgery and complementary treatment suggests that MRI cannot detect microscopic tumor tissue. The diagnosis between an inflammatory granuloma and a small residue is difficult and advances in imaging will make possible the detection of small residual tumors after a surgery.

Regarding the survival rate, there has been a tremendous evolution in the last decades. In 1986, we reported 24 patients with an EpPCF with a survival rate of only 2 (8,3%) out in 5 years (personal data). In 1991, Lyons *et al* reported in his series a 5-year survival rate of 14% for pediatric EpPCF[31]. In 2013, Cage reported an improved overall survival of EpPCF compared to supratentorial children [40]. The aggressive surgical approach contributes to a significant increase in the survival rate representing a favorable prognostic factor [5]. Our current series is in agreement with this as overall survival rate of our series was of 63,6%.

RADIOLOGICAL DIAGNOSIS:

MRI is the elective tool for diagnosis. The most frequent site of ependymoma is the fourth ventricle [17]. They extend to the cerebellopontine angle (CPA) through the Luschka foramen and/or to the great cistern through the Magendie foramen. We noted a high rate of lesions lateralized towards the CPA or towards the great cistern. Ependymomas are often calcified (50%)[17]. The T2 hypersignal permits to delimit lesions associated with cysts (20%). The enhancement with gadolinium is often heterogeneous. Hydrocephaly is common [23] and present in 45.45% of our cases. Each patient should have a cranio-spinal MRI before surgery [16]. Metastases at diagnosis are exceptional [17] and we only reported one case in this series. EpPCFs developed CSF seeding in one fourth of the case, and about 80% of positive CSF were high-grade lesions [24][25]. We did not find a preferred site of seeding of metastasis.

HYDROCEPHALY CONTROL

Generally, the resection of the tumor may be sufficient to manage obstructive hydrocephalus [26, 27]. In our series, an ETV was realized in 43.75% of patients before surgery to avoids high ICP during tumor resection and post-operative complications. ETV in infants with EpFCP [28] provides a reduction of shunts in our series. However, a shunt may be necessary despite ETV and surgical removal of the tumor. The CSF

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shunt was a palliative treatment in a child whose parents refused a new surgery seven months after the first approach for a recurrence in the fourth ventricle.

SURGICAL REMOVAL

In 10 studies involving 307 patients, a complete resection was performed in 29% of the 179 children with EpFCP [29]. Our rate of complete removal was of 78.1%. The surgical exploration of the fourth ventricle, also when tumors are localized in the CPA or at level of the occipital hole, is important to avoid incomplete resection that remains the strongest predictor of poor prognosis [8].

When tumors extend ventrally to the brainstem their complete resection is more difficult. Ependymomas remain a surgical disease and complete removal is responsible of postoperative sequels with facial nerve or mixes nerves palsies. Even in cases of infiltration of the floor of the fourth ventricle, a complete removal is possible and with a cottonoid a cleavage plane can be found to remove the tumor.

The bipolar, in case of bleeding, has to be avoided to prevent ischemic lesions of the floor. Three patients had incomplete removal in the group infiltrating the floor of the fourth ventricle, only one case needed a tracheostomy and a mechanical ventilation for one year. He died of a pneumopathy followed by a cardio respiratory arrest.

Five cases with a complete removal are alive, two patients with an incomplete removal progressed instead of a treatment with chemo and radiotherapy.

The second-look surgery increases the rate of complete removal improving the effectiveness of complementary treatments [5, 30]. An early surgery is important because a delay inferior to one month can be sufficient to avoid metastasis. This attitude should be systematic if the child is in good clinical condition after the 1st surgery and performed by an expert surgeon.

The overall survival is better in groups treated with complete surgery. Our series did not report peri or early postoperative mortality. Transient involvement of the mixed nerves were observed when ependymomas extend in the CPA, requiring careful dissection and dexterity of the surgeon to preserve cranial nerves very fragile and sensible to the dissection [31, 32]. Electrophysiology facilitates the removal providing an intraoperative assistance to respect anatomical structures. The dissection of the lateral wall of the brainstem or of the floor of the fourth ventricle is a source of sequels but, in our experience, also of a long-term survival.

Recurrences of EpPCF are frequent [5, 6, 33]. In our series, the recurrence rate was 50% and generally occurred in the first 3 years after surgery. The high recurrence rate in infants is explained by the fact that early age remains a worse prognostic factor compared to older children [34]. Duffner et al stressed that the low survival rate, in very young children, was related to the posterior fossa location rather than to the rate of complete resection or to the delay of radiotherapy as cerebellum, brainstem and the floor of the fourth ventricle are more sensible to the surgical aggression in young children [35]. Six out of ten young children were alive at 5 years of age without recurrence, underlining the importance of complete resection associated with radiotherapy.

The outcomes of the EpPCF with complete resection were better than in patients with subtotal resection and the statistical difference was significant (p[?]0.009). Outcome was better after total resection with 82.1% survival compared to 17.9% survival for patients with incomplete resection. Our series confirmed that posterior fossa ependymomas remains a surgical disease. The recurrence and mortality rate, despite multiple surgeries and current trials, push to a better genetic knowledge of this tumor to find more valuable therapeutic and prognostic markers.

CHEMOTHERAPY:

EpPCF is a chemoresistant tumor. The benefits of chemotherapy in infants are still debated. The high recurrence rate in our series confirms this again. Chemotherapy was mainly used to delay radiotherapy to systematically treat metastatic relapse and/or to reduce the radiation field. The interest of post-irradiation chemotherapy in EpPCF is being tested in randomized studies [16] and results are still unknown. Neoadjuvant

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chemotherapy is thought to have a potential, though unclear, role in the preparation of a second look to facilitate a total removal [33].

RADIOTHERAPY

Adult EpPCF can be cured by gross total resection without adjuvant treatment [4]. In children complementary treatment is required even after recurrence surgery. Focal radiation therapy is now considered as the "first line treatment" in children [30] : 54 to 59.4 Gy in fractions of 1.8 Gray on the tumor bed are performed as soon as possible after surgery. The surgery/radiotherapy delay averages 40 days in our series. A longer delay in two children was related to post-surgical sequels. Cerebral or spinal metastases can benefit from a focal irradiation of 45 to 54 Gy. In a series of 24 children over 5 years of age (20 infratentorial, 10 grade III and 16 with complete resection) treated with bi fractionated irradiation of 60 Gy in the case of complete resection and 66 Gy otherwise. OS and event-free survival at 5 years of age was 74% and 54% respectively [36] demonstrating the efficacy of radiotherapy in grade II EpPCF [37].

Protontherapy might explains the improvement in our series. Currently, ependymoma has become the most common pediatric tumor treated with proton therapy because it is associated with better progression-free survival [30]. Four out six of our patients who benefited from this technique presented no recurrence over 5 years. The re-irradiations after recurrences remains discussed and associated with sequels. Our series reports endocrine complications such as hypothyroidism and growth hormone deficiency related to the doses received on the pituitary gland and one patient presented a grade III alopecia. A pituitary dose limited to 20 grays and a limited thyroid irradiation of less than 1 gray are sufficient to avoid it [38]. Cognitive decline is a recognized effect of irradiation in children treated for posterior fossa tumors [39]. One of our patients presented physical and cognitive fatigue and neurocognitive sequels. Merchant *et al* advocated sparing the cerebellum as an important element in reducing the physical, psychological and intellectual sequel in school performance [39] shoving that the cerebellum tolerated the least radiotherapy [39].

QUALITY OF LIFE

Few studies report quality of life of children treated for EpPCF [5, 41]. New strategies should be discussed not only on survival rates but also on quality of life. The quality of life of young patients whome undergo several operations and their social and school life is a challenge for practitioners. Twenty-one patients alive have good overall motor function and daily life. Parents commented on the positive long-term outcome which was much better than expected and feared in the first years after the treatment. Two parents of children, now adults, reported the difficulties of jobs related to the slow execution of complex tasks involving several executive processes. A child operated twice (last time in 2010) was hampered in walking that was cautious. His father does not report difficulties in the fine gestures, his writing was neat but slower. This stressed that society should respect these patients who have difficulties in execution but who are able to do a well having adequate time.

Hanzlik *et al* [42] evaluated Intelligence Quotient performances of children treated for a central nervous system tumor (N=456) children with ependymoma had Intelligence Quotient deficits, but unlike medulloblastoma, their IQs did not deteriorate over time. Out of nine patients with Intelligence Quotient evaluation, in one the result was very good, in six it was normal and in two it shoved mild deficiency. The working capacity of our group was acceptable: regular schooling and school reintegration of children in primary schooling was easier than in secondary school, as observed in 8 patients enrolled in school without aid. Three children operated before 4 years old and still in school needed support from secondary school onwards. Four patients presented problems of graphism. Four students in University course were in normal program but three presented some difficulties. The verbal intelligence was normal in eight patients and limited in one patient. The relation between age at diagnosis and cognitive sequels was not demonstrated. The neuropsychological examination of children is reassuring with good intellectual skills as their peers. Avoiding irradiation of the supratentorial region limited neurocognitive impact compared to literature data from series where radiotherapy was retained indispensable.

Conclusion :

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Our series confirms that EpPCF is an aggressive tumor. Despite molecular studies, no valuable therapeutic targets have yet emerged. Surgery with complete removal remains the most important prognostic factor even if associated to an increased risk of postoperative deficits. Second-look surgery combined with proton therapy is highly correlated with improved survival. Thus, it is accepted that posterior fossa localization makes this disease different, in evolution and management, from ependymomas in other locations of the central nervous system. In the future, we hope to understand their genetic and biomolecular mechanisms and to find a chemotherapy or radiotherapy treatment more effective.

As for now, surgery for EpPCF must be aggressive to offer the best chances of a definitive cure for children also if responsible of an increased rate of sequels.

Disclosures: The authors report no conflict of interest

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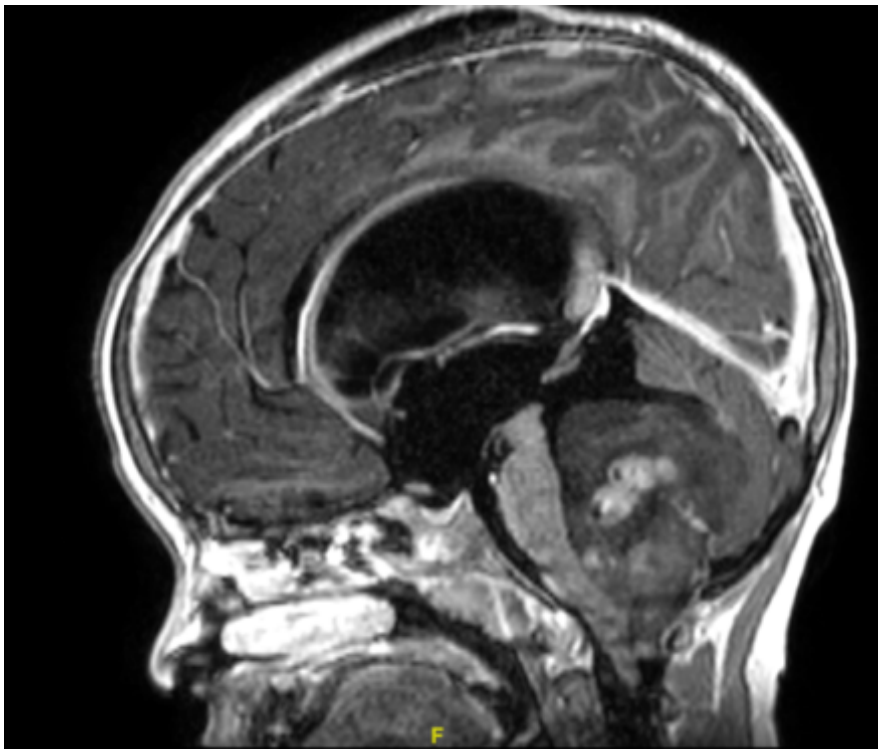
Figures Legends

Figure 1: Pre-operative (A) and post-operative (B) MRI scan in a sagittal 3D T1-weighted contrast after gadolinium injection showing A) a typical posterior fossa ependymoma and B) a complete removal of the lesion.

Figure 2: Kaplan-Meier survival curve in male and female showing no statistical difference ($p>0.05$).

Figure 3: Kaplan-Meier survival curve in grade II and III ependymoma showing no statistical difference ($p>0.05$).

Figure 4: Typical sagittal spinal 3D T1-weighted contrast after gadolinium injection showing a nodular L2L3 metastasis with a pial enhancement along the all medulla 8 months after the initial diagnosis.



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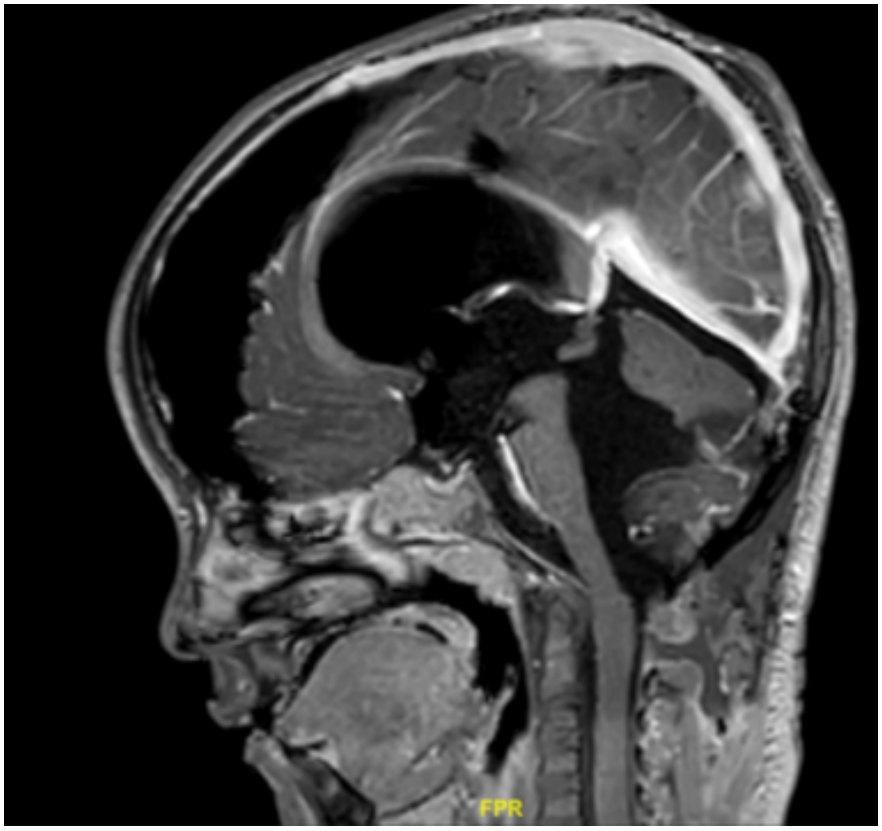

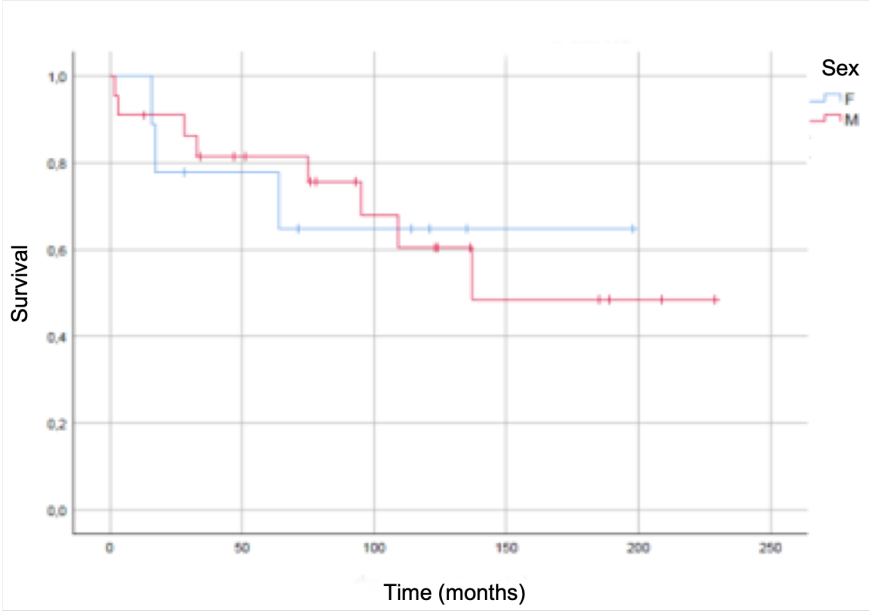

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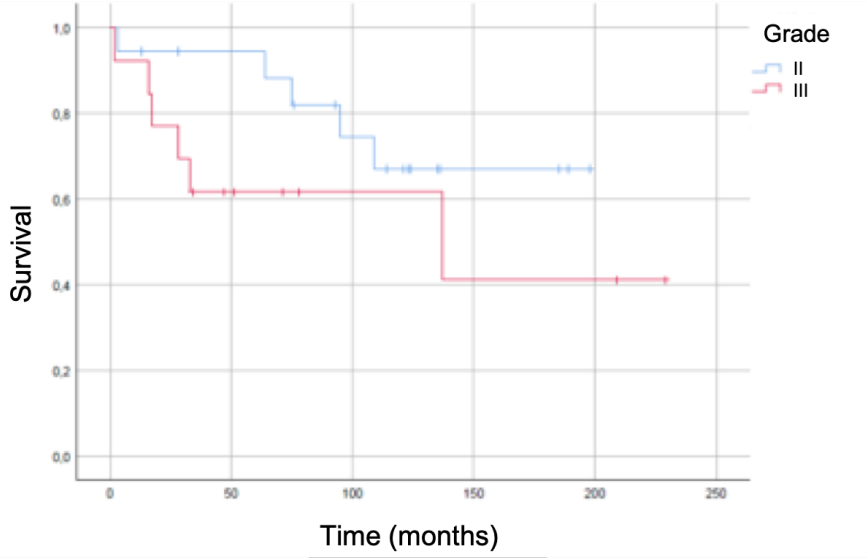

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