



# Clinical characteristics and long-term surgical outcome of spinal myxopapillary ependymoma: a French cohort of 101 patients

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## Abstract

**Purpose** Myxopapillary ependymoma (MPE) is the most frequent tumor affecting the medullary conus. The surgical therapeutic management is still debated and only few studies have focused on the postoperative clinical outcome of patients. This study aimed to demonstrate long-term postoperative outcome and to assess the predictive factors of recurrence as well as the clinical evolution of these patients.

**Methods** From 1984 to 2019, in four French centers, 101 adult patients diagnosed with MPE were retrospectively included.

**Results** Median age at surgery was 39 years. Median tumor size was 50 mm and lesions were multifocal in 13% of patients. All patients benefited from surgery and one patient received postoperative radiotherapy. Gross total resection was obtained in 75% of cases. Sixteen percent of patients presented recurrence after a median follow-up of 70 months. Progression free survival at 5 and 10 years were respectively estimated at 83% and 79%. After multivariable analysis, sacral localization, and subtotal resection were shown to be independently associated with tumor recurrence. 85% of the patients had a favorable evolution concerning pain. 12% of the patients presented a postoperative deterioration of sphincter function and 4% of motor function.

**Conclusion** Surgery alone is an acceptable option for MPE patients. Patients with sacral location or incomplete resection are at high risk of recurrence and should be carefully monitored.

**Keywords** Spinal tumor · Spine · Extramedullary tumor · Molecular biology · Radiation therapy · Recurrence

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## Introduction

Myxopapillary ependymoma (MPE) is a rare tumor, with an estimated incidence of 1 out of one million inhabitants [1]. The 2006 WHO classification assigned to MPE a grade 1, but the grade will be changed to grade 2 in the next classification [2, 3]. MPE occurred almost exclusively within the conus and the filum terminale [3]. MPE is the most frequent tumor of the conus medularis [3, 4]. The natural course of MPE remains largely unknown. Some articles on untreated MPE report an evolution towards tumor growth and neurological degradation within a few years [5, 6]. The average duration of symptoms preceding diagnosis ranges from 13 months to 8.3 years since they are slow growing [6–8]. Most patients present a long history of non-specific symptoms such as low back pain with or without motor, sphincter or sensory signs [9].

Surgical tumor gross total resection (GTR) is the gold standard treatment. The impact of adjuvant radiotherapy (RT) remains currently debated [9–11]. Young age, subtotal resection (STR) and capsule violation are described as unfavorable prognostic factors associated with tumor recurrence [12–15]. Few studies have evaluated the functional postoperative outcome [16].

This study aims to: (i) analyze patient and tumor characteristics as well as the long-term clinical outcome after surgery and (ii) clarify the management of recurrences.

## Methods

### Ethics Statement

The data collected during the study was stored in a computer file in accordance with the law of the French Data Protection Act of January 6, 1978 amended in 2004. The protocol can be found in the reference methodology MR003 chapter adopted by the Commission Nationale de l'Informatique et des Libertés (No 2219024 v0) in agreement with the policies of the University Hospitals involved in this project. In accordance with the ethical standards of our hospital's institutional review board, the Committee for the Protection of Human Subjects, and French law, written informed consent was not needed for demographic, physiological and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies; however, patients were informed of their inclusion in the study. The manuscript was prepared in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

## Patients

From 1984 to 2019, 101 patients with an histological diagnosis of MPE (according to the WHO classification of tumors of the central nervous system 2016 [3]) and treated in four French institutions were included in this study. Patients younger than 15 years of age, and patients who had a lack of data in their medical report were excluded.

All information regarding the patient, the clinical and the surgical procedures as well as periodic check-ups were anonymously extracted from medical records and analyzed by the authors. Patients' motor and sphincter dysfunctions were assessed using motor and urodynamic testing respectively that allowed comparisons between the pre- and postoperative periods. Radiological data were collected from reports or original images if available and included the number of vertebral segments affected, size and location of the tumor, presence of cyst, syringomyelia, bone scalloping, hemorrhage, T1- an T2- weighted MRI signal and gadolinium enhancement.

## Statistical analysis

All statistical analyses were performed with the software R (version 4.0.0, 2020-04-24), and figures with GraphPad PRISM 5.00. Age at the time of the surgery, gender, body mass index, tobacco use and, quality of resection were collected.

Resection was classified as GTR by radiologist if no residual tumor was seen on first injected postoperative MRI, 6 weeks after surgery, as near GTR for > 90% of tumor volume resection, as subtotal for 50–90% of tumor volume resection and partial for < 50% of tumor volume resection.

The tumor was defined as “large” if: (i) it measured more than 5 cm [17] or, (ii) when the size was unknown, if it extended over at least four vertebral bodies. Intraoperative bleeding, suspected pre-operative diagnosis, duration of surgery, blood transfusion, pre- and post-operative symptoms, time from first symptoms to surgery and outcome at last follow-up were also collected. For patients presenting recurrence, we registered the time from surgery to recurrence (progression free survival, (PFS)) as well as the location and treatment of the recurrence.

The age of male patients was significantly different from a normal distribution (Shapiro–Wilk test  $p=0.04$ ). Thus, age differences between men and women were analyzed with a Wilcoxon test. In order to determine the association between univariate factors and recurrence and for the calculation of odd ratios and 95% confidence intervals we used Fisher's exact test to analyze 2-way contingency tables.

To assess PFS we used Kaplan–Meier estimates with the “survival” package in R. Tumor recurrence represented the

events. We used the log-rank test to assess the influence of the different factors listed above on tumor recurrence. Factors achieving  $P \leq 0.05$  in our univariable analyses were entered into the multivariable model. Multivariable analysis was then performed using Cox stepwise regression analysis to define the independent contribution of each prognostic factor. Statistical tests were two-sided and  $P < 0.05$  defined statistical significance.

## Results

### Patient and tumor characteristics

One hundred and one patients were included. Patient characteristics are detailed in Table 1. Women were older than men (median = 45 vs 34 years,  $P = 0.004$ ). The lumbar localization was the most frequent (94%), more specifically the upper segments, as the L1, L2 or L3 vertebral levels were involved in 88% of patients. Thirteen patients (13%) presented multifocal MPE (2, 3 and 4 locations in 8, 3 and 2 patients respectively).

Pain was the main symptom: 90 patients (90%): 63 patients (62%) suffered from low back pain with radiculalgia, 19 patients (19%) isolated low back pain and eight patients (8%) isolated radiculalgia. A nocturnal exacerbation was described in 20% of the cases.

The other symptoms such as sphincter, motor and sensory dysfunctions were almost equally distributed (41%, 35% and 37% of patients respectively). Among patients with sphincter dysfunction, 83% had chronic or acute urinary retention, 35% had urinary incontinence, 34% complained of abnormal anal sphincter function and 15% of erectile dysfunction.

Onset was abrupt in 12 patients and six of them showed intratumoral hemorrhage on MRI. Furthermore, one of these patients presented a sudden headache caused by subarachnoid hemorrhage with negative digital subtraction arteriography. MRI signals were not specific, the most frequent pattern was an iso signal T1 and a hypersignal T2. However, Gadolinium enhancement was constant. Diagnosis of MPE was preoperatively evoked for 61 patients (66%).

### Surgical treatment

All patients underwent surgery. One patient (1%) underwent adjuvant radiotherapy. A GTR was achieved in 76 patients (75%). Near GTR was obtained in 8 patients (8%) and subtotal resection in 16 patients (16%). One (1%) patient had a partial resection. Dura matter was perforated by the tumor in 9 cases. GTR was obtained more frequently for solitary lesions compared to multifocal lesions (84% vs 15%  $P < 0.001$ ).

**Table 1** Patient characteristics

Variable (n = number of patients assessed)	Number (%)
Gender (n = 101)	
Male/Female	54/47 (53.5%/46.5%)
Age, years (n = 101)	
Median [range]	39.1 [15.7–77.8]
BMI (n = 96)	
< 25 / 25–30 / > 30	55 (57%)/31 (32%)/10 (10%)
Tobacco use (n = 95)	25 (26%)
Diabetes (n = 99)	7 (7%)
Symptoms	
Pain (n = 99)	90 (91%)
Motor deficit (n = 101)	35 (35%)
Sphincter dysfunction (n = 99)	41 (41%)
Sensory disorder (n = 100)	37 (37%)
Sudden onset (n = 101)	12 (12%)
Duration of symptoms, months (n = 93)	
Median [range]	11 [0.01–323]
Tumor location (n = 100)	
Thoracic	1 (1%)
Thoraco-lumbar	14 (14%)
Thoraco-lumbo-sacral	6 (6%)
Lumbar	60 (60%)
Lumbo-sacral	13 (13%)
Sacral	5 (5%)
Cranio spinal	1 (1%)
Multifocal lesions (n = 101)	13 (13%)
Tumor size (mm) (n = 75)	
Median, Mean, [range]	50, 71, [6–420]
Radiological characteristics	
Bone scalloping (n = 101)	8 (8%)
Syringomyelia (n = 101)	8 (8%)
Cysts (n = 101)	13 (13%)
Hemorrhage (n = 101)	7 (7%)
T1 weighted signal (n = 58)	
Hyper/iso/hypo/heterogenous	1/45/9/3
T2 weighted signal (n = 60)	
Hyper/iso/hypo/heterogenous	34/11/0/15
Treatment (n = 101)	
Surgery alone	100 (99%)
Surgery + adjuvant radiotherapy	1 (1%)
Gross total resection (n = 101)	76 (75%)
Surgical duration, min (n = 89)	
Median [range]	205 [25–700]
Blood loss, mL (n = 53)	
Median [range]	300 [30–2000]
Perioperative blood transfusion (n = 85)	10 (12%)
Dural perforation (n = 101)	9 (9%)
Capsule rupture (n = 49)	17 (35%)
Adhesion (n = 91)	
No or mild	48 (53%)
Important	43 (47%)

Values are expressed as number of patients (%) unless otherwise indicated

## Post-operative complications

Six patients presented a postoperative cerebro-spinal fluid leakage (two required surgical treatment), four patients had an infection of the operative site (two required surgical treatment), five patients developed a meningocele (three required surgical treatment), three patients had arachnoiditis (one of them required surgical treatment), and one patient developed pneumocephalus. Other non-specific complications were reported: one pulmonary embolism, one pulmonary atelectasis and one ileus.

## Clinical evolution

The median follow-up was 70 months [1–422]. No patient died during the follow-up. The evolutions of the main symptoms (motor dysfunction, sphincter dysfunction and pain) are summarized in Fig. 1. Most patients had functional improvement: 24/41 (59%) patients with sphincter dysfunction improved and 12/41 (29%) remained stable; motor function was improved in 24/35 (69%) patients and 7/35 (20%) were stable. Pain decreased or resolved in 76/90 (84%) patients.

Worsening of symptoms was recorded for 30 patients (30%) (Hypoesthesia  $n=14$ , motor function  $n=4$ , sphincter function  $n=12$ , pain  $n=3$ , deformation  $n=1$ ). All motor declines occurred in patients presenting a preoperative motor deficit. Postoperative sphincter deterioration was present in 12 patients, including seven with normal preoperative sphincter function. Three patients needed permanent self-catheterization, and the others had perineal hypoesthesia or occasional urinary incontinence. Age, sex, overweight, tobacco use, large tumor sizes and time from first symptom to surgery were not associated with increased risk of functional decline (motor or sphincter). Preoperative deficits and significant tumor adhesions seem to increase the risk

of functional deterioration, although results did not reach statistical significance ( $P=0.07$  and  $P=0.08$  respectively).

## Tumor recurrence

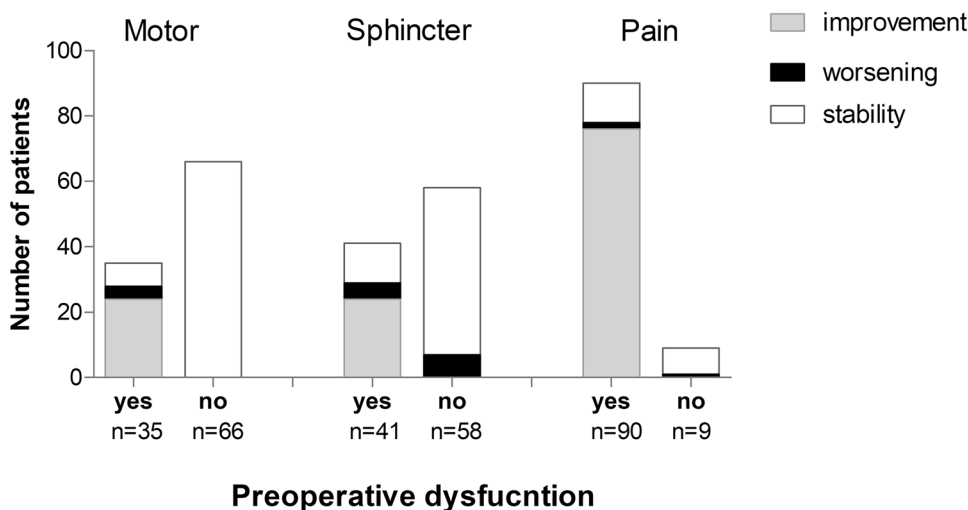
Recurrence occurred in 16 patients (16%). One of them underwent initial adjuvant radiotherapy. Data are summarized in Table 2. The median time to recurrence was 25 months. Two recurrences occurred for initially undiagnosed bifocal lesions. Thirteen patients (13%) presented a local recurrence and 3 patients (3%) a distant location. For five patients, recurrence was multinodular. PFS at 5 and 10 years were estimated at 83% and 79% respectively (Fig. 2).

## Factors associated with tumor recurrence

In univariable analysis, preoperative factors significantly associated with recurrence were: involvement of at least one sacral level (OR = 15.7 IC95% = [4.4–60.5],  $P < 0.001$ ), large tumors (OR = 6.3, IC95% = [1.56–27.5],  $P = 0.005$ ) and multifocal lesions (OR = 4.3, IC95% = [1.17–15.6],  $P = 0.03$ ). The intraoperative data that was significantly associated with recurrence were: subtotal resection (OR = 25 IC95% = [6.4–117],  $P < 0.001$ ), dural perforation by the tumor (OR = 8.9 IC95% = [1.6–52],  $P = 0.005$ ), transfusion or bleeding  $> 500$  cc (OR = 8.6 IC95% = [1.75–58.2],  $P = 0.002$ ), surgery  $\geq 3$  h (OR = 8.6 IC95% = [1.2–189],  $P = 0.03$ ) and substantial adherence (OR = 3.7 IC95% = [1.1–13.7],  $P = 0.045$ ) (Fig. 3 and Table 3). The recurrence rate was 4% (3/76 patients) in the GTR group versus 52% (13/25 patients) in the STR group.

The multivariable model (Table 3) retained incomplete resection (HR = 11.2 IC95% = [2.1–60.6],  $P = 0.005$ ) and the involvement of at least one sacral level (HR = 7.7

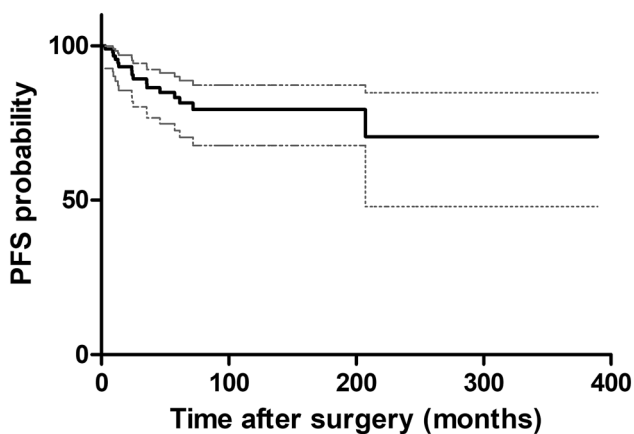
**Fig. 1** Clinical evolution depending on preoperative neurological status. The four patients with motor function decline had preoperative motor dysfunction. Sphincter dysfunction occurred in patients with or without preoperative dysfunction. Surgery relieved the pain in 85% of patients



**Table 2** Characteristics of patients with recurrence

Age	Tumor location	Tumor size (mm)	Nb of location	Initial treatment	Type of recurrence	PFS (mos)	Salvage treatment sequence	Status at last follow up
61	L1-L5	118	1	STR	Local	24	0 (refusal)	Paraplegia (32mos)
48	T12-L2	54	1	STR	Local	10	Surgery	Stable (119mos)
26	L3-L4, S1		2	STR	Spread	24	Surgery – Surgery + RT	Stable (122mos)
73	L2-S2	171	1	STR	Local	11	RT	Stable (67mos)
31	T10-L2, L4		2	STR	Local	24	Surgery	Stable (89mos)
33	T12, L2, S1-S2	43	3	STR	Spread	71	RT	Stable (184mos)
32	Intra-cranial, L3L4, L5S2	165	3	STR	Spread	3	Temodal	Tumor progression (22mos)
57	L3-L4, L5-S2		2	STR	Spread	46	Active surveillance	Tumor progression (46mos)
73	T7-S1	250	1	STR	Local	36	0 (refusal)	Paraplegia (97mos)
56	S3-S5	63	1	STR	Local	9	Surgery – RT	Stable (36mos)
46	T6-L5	420	1	STR	Local	36	Surgery + RT	Stable (276mos)
40	L2-S2	90	1	GTR	Local	58	Surgery × 3	Stable (221mos)
40	L5-S2	50	1	STR	Local	25	Surgery – Surgery + RT	Stable (118 mos)
16	L3-S3	140	1	GTR	Spread	13	Surgery	Stable (116mos)
23	T12-S2		1	STR + RT	Spread	207	Active surveillance	Stable (422mos)
28	L5-S2	30	1	GTR	Local	61	Surgery	Stable (262 mos)

STR subtotal resection, GTR gross total resection, RT radiotherapy, PFS progression free survival



**Fig. 2** Progression free survival (PFS) analysis. Kaplan–Meier estimation of progression free survival and the 95% confidence intervals

IC95%[1.8–32.7],  $p=0.005$ ) as being independently associated with tumor recurrence.

### Management of recurrence

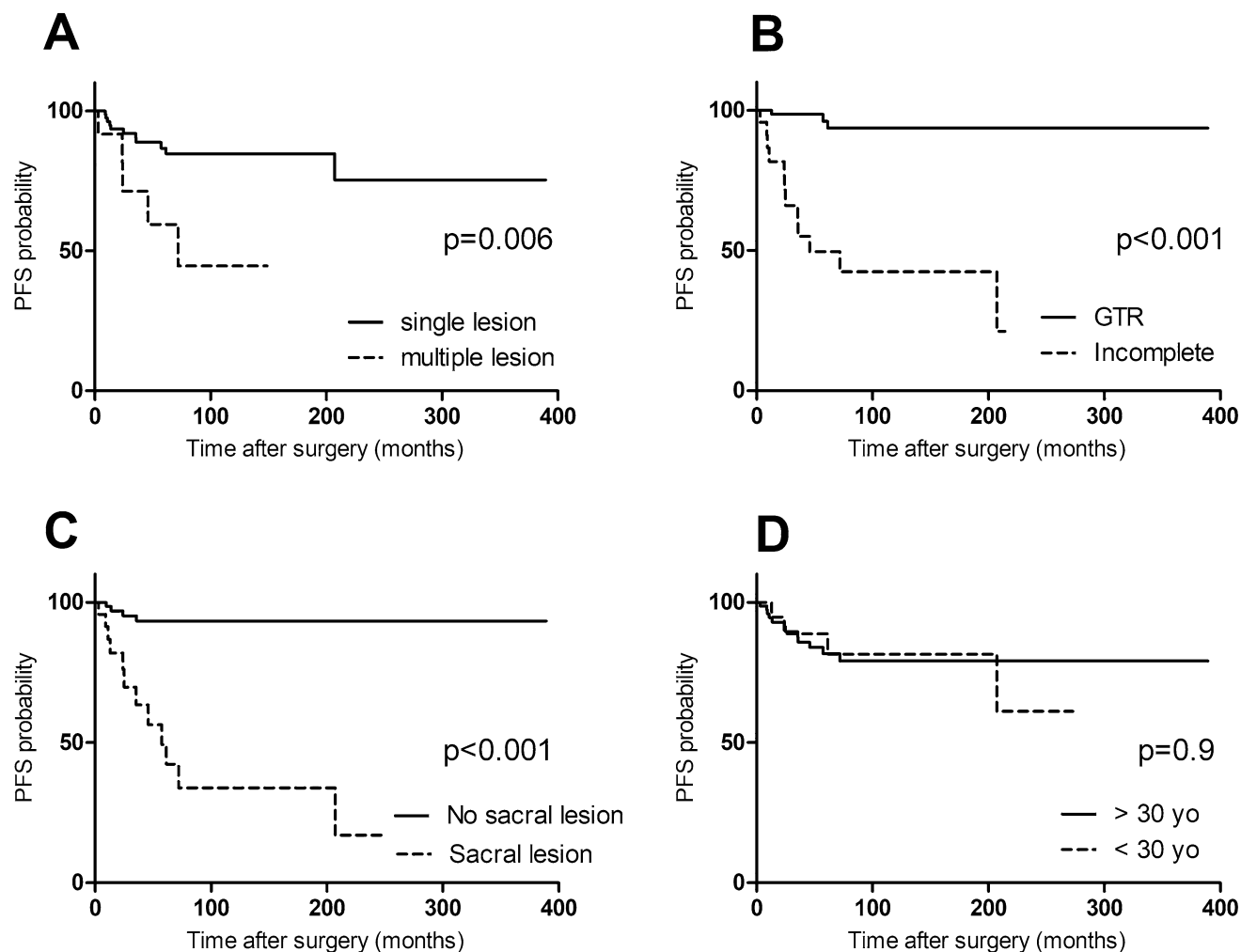
Among 16 recurrences (16%), 8 (50%) were treated with a second surgery, 2 (12.5%) with radiation therapy, 1 (6%) by surgery associated with radiotherapy, 1 (6%) with

chemotherapy (temozolomide), and 2 (12.5%) followed by close monitoring. Two patients refused treatment, and both deteriorated to complete paraplegia. Four patients (25%) treated with surgery developed a new recurrence requiring additional treatment (radiotherapy and/or surgery). Tumors were controlled at last follow-up in 12/16 patients (75%) (Table 2).

## Discussion

### Surgery

In most cases, a GTR was obtained. With this attitude, despite larger tumors than those classically described, our recurrence rate (16%) and PFS at 5 and 10 years was comparable or lower than those described in the literature although median tumor size is larger [9–11, 18]. However, in our study, the rate of GTR was higher than that found in the literature. This factor is important in limiting the risk of recurrence (4% in the GTR group versus vs 52% in the STR group in our study) It is not possible to determine whether the good results of this series are related to our therapeutic strategy (no adjuvant radiotherapy) or to the high rate of GTR.



**Fig. 3** Progression free survival (PFS) analysis of patients according to different prognosis factors. **a** PFS curve for patients with multiple lesions compared to a unique lesion. **b** PFS curves of patients with or

without gross total resection. **c** PFS curve of patients with or without a sacral lesion. **d** PFS curve of patients younger than 30 years old compared to patients aged 30 years old or more

### Clinical evolution and toxicity

The postoperative evolution was marked by an improvement in pain levels for almost all patients. Motor and sphincter disorders were partly or completely improved in most patients independently of the duration of the symptoms. This surgery has a rather high postoperative complication rate. Nearly a third of patients had a neurological complication. Most often it is a well-tolerated sensory deficit. Only patients with preoperative motor deficits showed an aggravation of their motor symptoms. It is important to note that the bladder function of a significant amount of the patients was impaired, including patients with no sign of such disorder before surgery. However, not all patients underwent a preoperative urodynamic assessment. Therefore, surgeons need to warn their patients of this risk.

### Recurrences

Risk factors for recurrence included classic factors such as incomplete resection or multiple locations. Age under 30 or 35 is a commonly described as unfavorable prognostic factor, but studies generally combine pediatric and adult populations [15, 18]. In our study, focused on adult population, young adults under 30 years do not appear to be more prone to recurrence than other patients. Therefore, it does not seem legitimate to propose a different treatment for this age category. In this study, intraoperative capsular infraction did not appear to be a negative risk factor, although this information was not included in all the records.

It is interesting to note that sacral location represents a strong risk factor for recurrence. Biomolecular analyses could be of interest to determine whether sacral tumors



**Table 3** Univariable and multivariable analyses of recurrence-associated factors

	Univariable analysis			Multivariable analysis		
	HR	CI 95%	<i>P</i>	HR	CI 95%	<i>P</i>
Patient characteristics						
Female	1.18	0.35–3.97	0.79			
Age < 30 years	1.33	0.28–5.15	0.74			
Tobacco use	0.92	0.19–3.5	1			
Overweight	1.31	0.36–4.6	0.78			
Tumor characteristics						
Sacral level	15.7	4.4–60.5	<b>&lt; 0.001</b>	<b>7.7</b>	<b>1.8–32.7</b>	<b>0.005</b>
Thoracic level	2.7	0.81–9	0.1			
Dural perforation	8.9	1.6–52	<b>0.005</b>	0.4	0.1–2.0	0.29
Large tumor	6.3	1.56–27.5	<b>0.005</b>	0.9	0.2–4.2	0.09
Multifocal	4.3	1.17–15.6	<b>0.03</b>	0.3	0.06–1.6	0.15
Surgery						
Incomplete resection	25	6.4–117	<b>&lt; 0.001</b>	<b>11.2</b>	<b>2.1–60.6</b>	<b>0.005</b>
Transfusion/bleeding > 500 cc	8.6	1.75–58.2	<b>0.002</b>		NA	
Duration ≥ 3 h	8.6	1.2–189	<b>0.03</b>		NA	
Substantial adherence	3.7	1.1–13.7	<b>0.045</b>		NA	
Capsula effraction	1.4	0.23–10.9	1			

Sacral level: at least one sacral level is involved. Thoracic level: at least one thoracic level is involved

present different molecular profiles, particularly concerning the expression of genes involved in cranio-caudal development. Previous work has been done on the HoxB13 gene that is expressed during the development of the terminal filum [19]. After the early embryonic stages, Hoxb13 is no longer expressed in the terminal filum nor in the spinal cord of healthy subjects [20]. Molecular profiling of ependymomas has shown that high expression of Hox genes in spinal ependymomas compared to intracranial localizations [21]. In addition, HoxB13 gene expression is a sensitive and specific marker of MPE in spinal cord tumors [20, 22]. The HoxB13 gene is known to be involved in various tumors of the pelvic region [23]. It would therefore be interesting to evaluate the expression of this gene in MPE with recurrence as well as in sacral localized MPE. To the best of our knowledge, no biomolecular factor has ever been associated with tumor recurrence. In our study, proliferative index (Ki67 / MIB-1) was not associated to recurrence.

Our study confirms data from the literature underlining the need of GTR in order to reduce the risk of recurrence. However, it cannot always be achieved, especially for multifocal tumors associated with increased risk of recurrence. In patients treated with GTR, only two developed recurrence. One had a giant tumor (140 mm) and the other had a sacral localization (L5-S2). It is thus necessary to reassure patients treated with GTR. One of the patients had a cervical distal recurrence. It seems appropriate to perform in patients at risk of recurrence (incomplete resection, giant or multifocal tumor...) a follow-up including pan-medullary MRI. In two patients the bifocal nature of the tumor had not been

diagnosed preoperatively, and only one of the two lesions was removed. These two patients developed recurrence. It therefore seems important to search carefully for multiple locations.

### Therapeutic strategy

The appropriate timing of surgery is still debated as this tumor is benign with a slow evolution. Most patients recover from their preoperative symptoms and the postoperative complication rate cannot be neglected, especially sphincter dysfunctions. Offering a close clinical and radiological monitoring to patients with drugs-controlled symptoms could be of interest [24]. Surgery should be considered on a case-by-case basis and recommended only to patients with disabling symptoms or radiological proof of tumor progression. However, in such a case, patients should not be lost to follow-up. Since only few insights into the natural course of these tumors are described in medical literature, the risk would be to let giant lesions develop, which would eventually be surgically challenging.

Despite the 35 year-period of analysis, few changes were noticed in the management of patients. All patients but one had preoperative MRI. All patients with a follow-up had serial MRI. The surgical technique described in operative reports did not change except dural sealing (fibrin sealant). No patient had intraoperative neuromonitoring. It could have been helpful for invasive tumors in order to maximize the GTR rate and minimize postoperative complications.

However, most of the aggravations involved sphincter functions and not motor functions.

The interest of systematic adjuvant radiotherapy after incomplete resection is debated. In our series, half of the patients who received an incomplete resection had recurrences, including the one patient who had received adjuvant radiotherapy. However, it is interesting to note that all the patients with recurrence who accepted salvage treatment are now controlled, except one who was multimetastatic from the outset. Our attitude is therefore to keep radiotherapy as a treatment option in cases with non-operable recurrences or as an adjuvant to salvage surgery. However, Akyurek et al. concluded that adjuvant RT appeared to significantly reduce the rate of tumor progression [13], while Pica et al. stated that only postoperative high-dose RT reduced the risk of recurrence [11]. Only results provided by a randomized controlled trial comparing surgery versus surgery plus RT could bring the debate to a conclusion.

The two patients who refused treatment for their recurrence declined to paraplegia. It therefore seems essential to monitor patients carefully over a long period of time, as late recurrences are not uncommon and early management of recurrences may be easier.

## Limitations

First, due to the low incidence of this tumor, our study is retrospective. Some data is missing, and some patients were lost to follow-up. Monitoring of symptoms before and after surgery seems to be a major factor to consider in this benign tumor. Being a retrospective study, data was extracted from medical records and there was no validated clinical score scale. Second, only one patient received first-line adjuvant radiotherapy. We cannot therefore compare efficacy of surgery versus radiotherapy. Due to the low incidence of this tumor, it is difficult to gather a large cohort of patients. This work focuses on 101 cases which is one of the largest clinical study with that from Weber et al. [10].

## Conclusion

Surgery alone demonstrates good results concerning the treatment of MPE, even for young adults. GTR is strongly associated with a lower rate of recurrence. Patients with sacral or multifocal lesions are highly prone to recurrence. Further biomolecular studies may be of interest to understand inter-tumor heterogeneity.

**Author contributions** A.S.M and B.M. Conceptualization; A.S.M and B.M. methodology; all the authors. validation; A.S.M., F.Be. and B.M.

formal analysis; A.S.M., S.T., G.L., S.G., M.P., C.A., F.P., A.I., L.F., F.Bi and B.M. investigation; B.M. resources; A.S.M., S.T., G.L., S.G., M.P., C.A., F.P., A.I., L.F., F.Bi and B.M. data curation; A.S.M., A.A. and B.M. writing—original draft preparation; all the authors writing—review and editing; B.M. and A.C. supervision. All authors have read and agreed to the published version of the manuscript.

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**Data availability** Anonymized data will be shared on request from any qualified investigator.

## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** The protocol can be found in the reference methodology MR003 chapter adopted by the Commission Nationale de l'Informatique et des Libertés (No 2219024 v0) in agreement with the policies of the University Hospitals involved in this project.

**Consent to participate** In accordance with the ethical standards of our hospital's institutional review board, the Committee for the Protection of Human Subjects, and French law, written informed consent was not needed for demographic, physiological and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies; however, patients were informed of their inclusion in the study.

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