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INTRACRANIAL AND SPINAL EPENDYMOMA

Series at Faculdade de Medicina, Universidade de São Paulo.

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Abstract – **Objective:** Ependymomas are rare intracranial neuroepithelial tumors and the most common location is intramedullary. The aim was to analyze the characteristics of these tumors to determine the patients' overall survival and the likelihood of recurrence. **Method:** Data of clinical presentation, tumor location, duration of symptoms, degree of resection and complementary treatment of 34 patients with intracranial ependymoma and 31 with intramedullary ependymoma who underwent surgery in the last ten years were collected and correlated with the recurrence time and overall survival. **Results:** There was statistically significant correlation between the degree of resection and intracranial tumor location, although it is not a hallmark of recurrence. Data analyses of intramedullary ependymoma did not show correlation with overall survival and likelihood of recurrence. **Conclusion:** The location of the intracranial tumor is connected with the degree of resection; however it is not a predictive factor to overall survival.

KEY WORDS: brain tumor, intramedullary tumor, ependymoma.

Ependimoma craniano e de medula espinhal: casuística da Faculdade de Medicina da Universidade de São Paulo

Resumo – **Objetivo:** Os ependimomas são tumores neuroepiteliais raros na localização intracraniana, porém um dos mais freqüentes na medula espinhal. Os autores analisaram as características destes tumores para determinar a sobrevida e probabilidade de recidiva nos pacientes. **Método:** Elementos da apresentação clínica, localização da lesão, duração de sintomatologia, grau de ressecção e tratamento complementar de 34 doentes com ependimoma intracraniano e 31 de medula espinhal operados nos últimos dez anos foram revisados e correlacionados com o período para a ocorrência da recidiva e a sobrevida. **Resultados:** Houve correlação estatística apenas entre o grau da ressecção e a localização dos ependimomas intracranianos, embora, este não se tenha mostrado um marcador de recidiva. A avaliação dos dados clínicos dos pacientes com ependimoma medular não permitiu definir correlação com a sobrevida e sobre a probabilidade de recorrência. **Conclusão:** A localização do tumor intracraniano está relacionada ao grau de ressecção, entretanto isso não foi um fator preditivo para a sobrevida.

PALAVRAS-CHAVE: tumor cerebral, tumor intramedular, ependimoma.

Ependymomas are rare tumors of neuroectodermal origin. They may arise from the ependymal cells of *filum terminale*, or from the cells that cover the central canal of the spinal cord or ventricular surface, or from the cells of the adjacent white matter to the ventricular surface, and fetal residual ependymal cells which migrate from periventricular regions[1,2].

Overall, they account for 6–9% of the intracranial tumors. They are the third most common tumor in the youngest age group, representing 30% of the intracranial primary neoplasms in individuals with less than three years of age[3]. Intramedullary spinal ependymomas are more common in individuals with 15 to 40 years of the age, representing about 30% of the ependymomas of the central nervous system and 60% of the intramedullary tumors[4].

Clinical presentation is non-specific and depends on

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the patient's age and the tumor location. Duration of the symptoms until diagnosis varies from one month to three years, generally being from three to six months[5]. Diagnosis is complemented by computerized tomography or magnetic resonance scanning of the central nervous system with image samples varying because of calcification presence, cystic or solid areas, microscopical areas of hemorrhages, necrosis, etc.

The aim of this study is to define the characteristics of the population of patients who had undergone surgery in last the ten years and to correlate them with overall survival and the probability of recurrence to determine hallmarks of prognosis.

METHOD

Thirty-four patients with intracranial ependymoma and 31 with intramedullary spinal cord or cauda equine ependymoma that were consecutively submitted to surgery in the Hospital das Clinicas at Faculdade de Medicina, Universidade de São Paulo from 1997 to 2007 have been assessed.

Table 1. Patients' gender, age, clinical presentation, time between symptoms onset and surgery, tumor location, degree of resection, complementary treatment, time from surgery to recurrence, tumor location at recurrence and death status in patients with intracranial ependymoma at age between 0–15 years.

Patient and gender	Age (years)	Clinical presentation	Time between symptoms onset and surgery (months)	Tumor location	Degree of resection	Complementary treatment	Recurrence	Time from surgery to recurrence (months)	Tumor location at recurrence	Dead
Between 0–15 years										
1,M	15	high ICP	47	infratentorialzz	subtotal (invaded the brainstem)	yes (RT + QT)	no	–	–	no
2, F	4	focal + high ICP	4	infratentorial	partial (stopped because of bleeding)	no	no	–	–	yes
3, M	1.5	focal + high CP	6	infratentorial	total	no	yes	1	infratentorial	no
4, F	1.5	focal	2	infratentorial	partial	no	no	–	–	no
5, F	3	high ICP	1	infratentorial	total	yes (RT)	yes	9	Conus medullaris	no
6, M	2	focal	8	infratentorial	partial (invaded the brainstem)	yes (QT)	no	–	–	no
7, F	9	high ICP	4	infratentorial	partial (invaded the brainstem and cranial nerves)	yes (RT before surgery)	no	–	–	no
8, F	13	high ICP	5	supratentorial	total	no	no	–	–	no
9, M	6.5	high ICP	3	supratentorial	partial	yes (QT + RT)	yes	8	supratentorial	no
10, M	9	seizure + focal + high ICP	2	supratentorial	total	yes (craniospinal RT)	yes	90	same location	no
11, M	5	focal + high ICP	3	supratentorial	total	no	yes	18	same location	no
12, F	3.5	focal + high ICP	2	supratentorial	partial	yes (QT)	no	–	–	no
13, M	2.5	focal	4	supratentorial	total	no	no	–	–	no
14, M	3.5	focal + high ICP	10	supratentorial	total	no	yes	31	infratentorial	no
15, M	6	focal	3	supratentorial	total	yes (QT + RT)	yes	17	supratentorial	yes
16, F	7	ICP	1	supratentorial	total	yes (RT before 2nd surgery)	yes	6	supratentorial	no
17, F	12	seizure + focal + high ICP	4	supratentorial	total	yes (RT)	no	–	–	no
18, F	0.5	seizure + high ICP	1	supratentorial	total	no	no	–	–	yes

M: male; F: female; ICP: increased intracranial pressure; focal: motor deficits (paresis); seizure: partial seizure or generalized seizure; RT: radiation therapy; QT: chemotherapy; RFTP: right fronto temporoparietal.

Table 1 (continuation). Patients' gender, age, clinical presentation, time between symptoms onset and surgery, tumor location, degree of resection, complementary treatment, time from surgery to recurrence, tumor location at recurrence and death status in patients with intracranial ependymoma at age over 15 years.

Patient and gender	Age (years)	Clinical presentation	Time between symptoms onset and surgery (months)	Tumor location	Degree of resection	Complementary treatment	Recurrence	Time from surgery to recurrence (months)	Tumor location at recurrence	Dead
19, M	46	visual + high ICP	2	infratentorial	total	no	no	–	–	no
20, F	51	high ICP	1	infratentorial	total	no	no	–	–	no
21, M	23	visual + high ICP	16	infratentorial	subtotal (invade the brainstem)	yes (RT)	yes	50	infratentorial	no
22, F	25	visual + high ICP	4	infratentorial	partial (invade the brainstem)	yes (craniospinal RT)	yes	1	same location	yes
23, F	34	visual + focal + high ICP	6	infratentorial	total	yes (RT)	no	–	–	no
24, F	41	high ICP	3	infratentorial	subtotal	yes (QT)	no	–	–	
25, M	28	visual + high ICP	1	infratentorial	subtotal (invade the floor of fourth ventricle)	no	no	–	–	yes
26, M	45	high ICP + nerves	24	infratentorial	partial (invade the brainstem)	yes (RT)	no	–	–	yes
27, F	27	high ICP + cerebellar	1	infratentorial	subtotal (invade the brainstem)	no	no	–	–	yes
28, F	73	high ICP	5	supratentorial	total	yes (QT + RT)	yes	1	R FTP	no
29, F	18	seizure + high ICP	8	supratentorial	total	no	no	–	–	no
30, F	24	seizure + high ICP	36	supratentorial	total	no	no	–	–	no
31, F	22	seizure + focal + high ICP	8	supratentorial	total	yes (RT)	yes	28	same location and supratentorial	no
32, M	42	Focal	2	supratentorial	total	yes (RT)	no	–	–	no
33, F	17	High ICP	6	supratentorial	subtotal	yes (RT)	no	–	–	no
34, M	42	High ICP	43	supratentorial	total	no	no	–	–	no

M: male; F: female; ICP: increased intracranial pressure; focal: motor deficits (paresis); seizure: partial seizure or generalized seizure; RT: radiation therapy; QT: chemotherapy; RFTP: right fronto temporoparietal.

Data of the clinical presentation, tumor location, duration of the symptoms until the surgery, degree of resection, complementary treatment were collected and are presented in Tables 1 and 2. Data of intracranial ependymomas in children and adults and spinal cord ependymomas are presented in separate tables and were correlated with the location of the tumor and the recurrence time and overall survival. SPSS v.15 was used for the statistical analyses of intracranial and intramedullary subgroups to define the possible prognostic factors.

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RESULTS

The mean age of the patients with intracranial ependymoma was 19 years (6 months to 73 years) (Fig 1A). Nineteen patients were female (55.8%) and the location was infratentorial in 47.1% of them. The most common symptoms were only increased intracranial pressure (ICP) (28.1%) or ICP elevation associated with focal neurological deficits (25%). Focal deficit was the only symptom in 15.6% of these patients. Visual complaints associated with elevated ICP symptoms were present in 12.5% of cases. Seizures occurred only in supratentorial tumors; in 9.4% of cases it was associated only with increased ICP and in 9.4% of cases it was also associated with focal deficits. The mean time between symptoms onset and the surgery was 8 months (1 month to 4 years). The correlation between location and the symptom with mean time be-

Table 2. Patients' gender, age, clinical presentation, time between symptoms onset and surgery, tumor location, degree of resection, complementary treatment, time from surgery to recurrence, tumor location at recurrence and death status in patients with intramedullary and conus medullaris ependymoma.

Patients and gender	Age (years)	Clinical presentation	Time between symptoms onset and surgery (months)	Tumor location	Degree of resection	Complementary treatment	Recurrence	Time from surgery to recurrence (months)	Tumor location at recurrence	Dead
1, M	22	pain	104	C3–T4	total	no	no	–	–	no
2, M	43	pain + deficit	34	C2–C5	total	no	no	–	–	no
3, F	39	deficit	44	C4–C5	partial	no	no	–	–	yes
4, F	28	deficit	22	C4–T4	total	no	no	–	–	no
5, M	31	dysesthesias + deficit	124	C2–C7	total	no	no	–	–	no
6, M	30	dysesthesias + deficit	11	C2–T1	total	no	no	–	–	no
7, F	22	pain + deficit	65	T6–T8	total	no	yes	40	same location	no
8, F	50	dysesthesias + deficit	12	T10–T11	total	no	no	–	–	no
9, M	18	dysesthesias + deficit	16	T12–L5	total	no	no	–	–	no
10, M	19	pain	17	C1–C4	total	no	no	–	–	no
11, F	33	pain + deficit	123	C3–T3	total	no	no	–	–	no
12, M	32	pain + deficit	6	T11–L4	partial	no	no	–	–	no
13, F	27	dysesthesias + deficit	39	T1–T3	total	no	no	–	–	no
14, F	23	pain + deficit	8	C5–T9	partial	no	yes	1	posterior fossa (partial resection)	no
15, M	42	pain + dysesthesias	52	T12 + conus medullaris	total	no	no	–	–	no
16, M	21	pain	36	filum terminale	partial	no	no	–	–	no
17, M	22	deficit	43	T9–T11	total	no	no	–	–	no
18, F	9	pain + deficit	10	T10–L3	total	yes (RT)	yes	3	same location e craniospinal seeding	yes
19, F	35	dysesthesias + deficit	28	C4–T2	total	no	no	–	–	no
20, F	60	pain + deficit	10	T9–T11	subtotal	no	yes	48	same location	no
21, F	9	deficit	9	C1–C6	total	yes (QT + RT)	yes	29	CPA and supratentorial; craniospinal seeding	no
22, M	63	dysesthesias + deficit	8	T5–T10	subtotal	no	no	–	–	no
23, F	43	pain	28	T12 + conus medullaris	partial	no	yes	60	Same location	no
24, F	49	pain + deficit	35	T1–T2	total	no	no	–	–	no
25, M	58	pain + deficit	44	C4–C7	total	no	no	–	–	no
26, F	12	pain + deficit	6	T3–T6	total	yes	yes	5	same location e craniospinal seeding	no
27, F	45	pain	13	T9–T12	total	no	no	–	–	no
28, M	19	deficit	5	C3–C7	total	no	no	–	–	no
29, F	28	deficit	1	conus medullaris	total	no	no	–	–	yes
30, M	33	pain + deficit	4	filum terminale	total	No	no	–	–	no
31, M	36	pain + dysesthesias	8	C3–C5	total	No	no	–	–	no

M: male; F: female; deficit: motor deficits (tetra– or paraparesis); C: cervical; T: thoracic; L: lumbar; RT: radiation therapy; QT: chemotherapy.

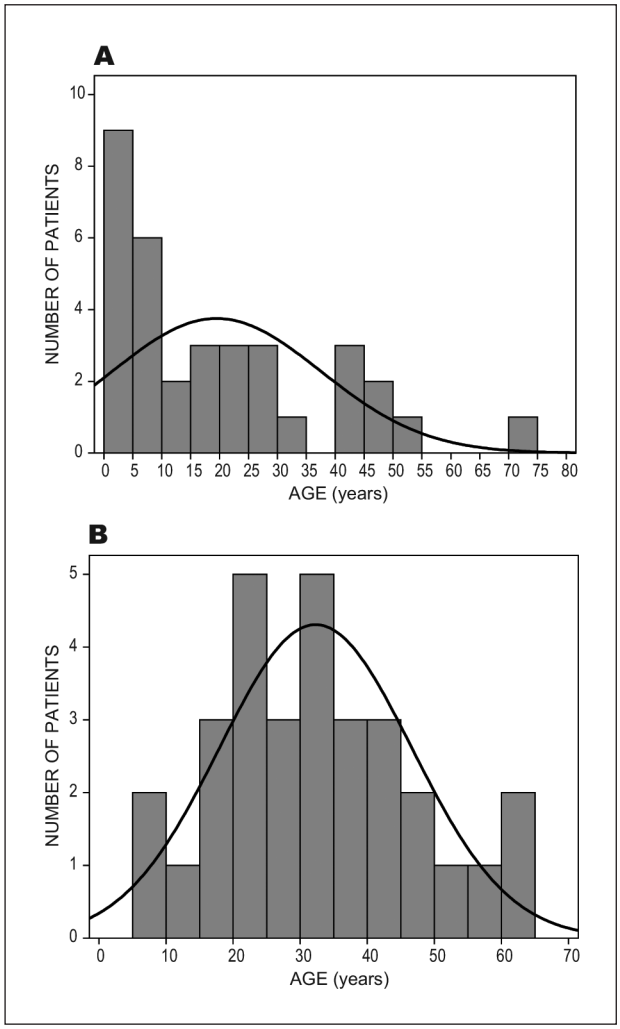

Fig 1. Age frequency of the patients with intracranial [A] and intramedullary [B] ependymoma at the time of first surgery.

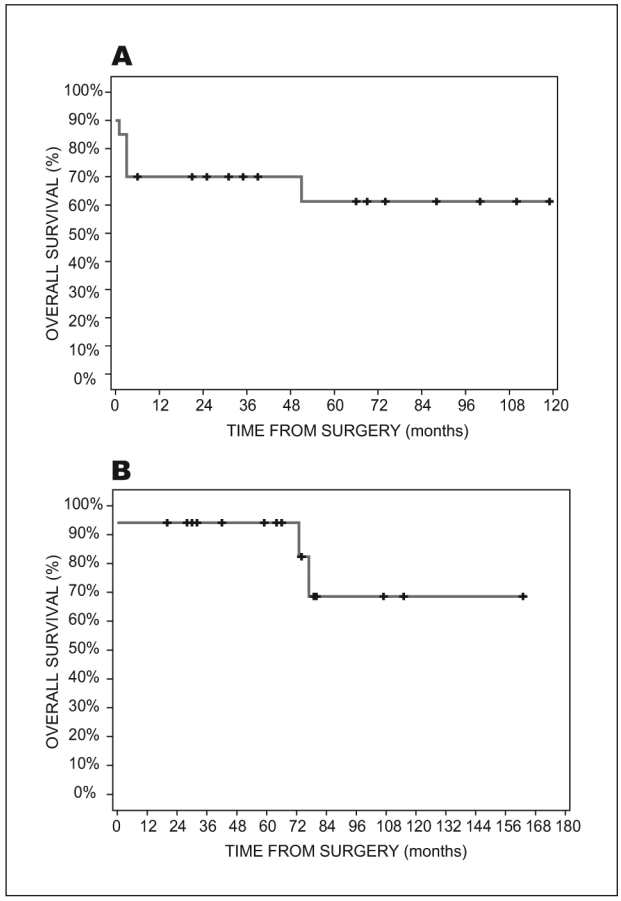

Fig 2. Overall survival (Kaplan-Meier survival curve) before first surgery until death or the last follow-up in patients with intracranial [A] and intramedullary ependymoma.

tween symptoms onset and the surgery was not statistically significant (p=0.805 and p=0.623, respectively).

The gross total resection was achieved in 58.8% of cases; supratentorial in 83.3% of cases and infratentorial in only 31.5% of cases. Follow-up ranged from 1 to 120 months (mean of 38 months). The 2-year survival was 70%, and 5-year survival was 60%, calculated by Kaplan-Meier method (Fig 2A).

Twelve patients with intracranial ependymoma recurred; 8 at the primary site, ranging from one to 90 months after surgery (mean of 21 months). The adjuvant therapy with chemotherapy or radiotherapy was indicated in 55.9% of the patients either when the tumor had subtotal resection or if it recurred. No association was noticed between the degree of resection and the tumor location with recurrence or survival. Also, there was no statistically significant correlation between survival and gender or patients' age in cases of intracranial ependymoma.

The age of patients with intramedullary ependymoma ranged from 9 to 63 years (mean of 32 years) (Fig 1B). Fifteen patients were female (48.4%). The time between the onset of symptoms and surgery ranged from one month to 10 years (mean of 31 months). The symptom of neurological deficit (tetra- or paraparesis) was present in 80.7% cases, and associating painful aching sensations with neurological deficit was more common (38.7%). Neurological deficit was the only symptom in 19.4% cases; it was associated with other sensory symptoms, such as dysesthesias, in 22.6% of cases. The symptoms of sensory disturbances were only pain and association of pain and dysesthesias in 12.9% and 6.5%, respectively. The more commonly affected site was thoracic (29%) and cervical cord (25.8%); only in 9.7% of the cases the location was exclusively in the *conus medullaris* and *filum terminale*. The lesions were present in the cervico-thoracic and thoraco-lumbar transition in 19.4% and 16.1% of the population, respectively. No correlation was observed between the location and the clinical presentation with the duration of symptoms until surgery (p=0.362 and p=0.835, respectively).

The gross total resection was achieved in 77.4% cases of intramedullary ependymoma and there was no correlation between the location and the degree of resection (p=0.362). The cause of subtotal resection was the lack of tumor limits or the linkage between tumor and normal tissue. There were no sensory or motor evoked potentials (MEP) used throughout the procedure. The tumor grade was myxopapillary ependymoma (WHO grade I) in 5 cases in lumbar or thoraco-lumbar location; all other were ependymoma (WHO grade II). Follow-up ranged from one month to 10 years (mean of 53 months). The 5 and 10-year survival was about 90% and 70%, respectively (Fig 2B), according to Kaplan-Meier analysis. Recurrence occurred in seven cases (31.8%), four of them being at the primary site. No correlation was identified between the degree of resection and recurrence (p=0.124). The time to recurrence ranged from 1 to 60 months (mean was 23 months). Adjuvant therapy was not routinely indicated, even in subtotal resection. Only three cases had radiation therapy indicated due to dissemination (two cases) and rapid recurrence (one case, 3 months after first surgery). The statistical analysis failed to identify any factor related to recurrence or survival.

DISCUSSION

Most reported series of ependymoma are retrospective and include only a small number of patients. Additionally, studies have been conducted over several decades, making it difficult to interpret results since classification and treatment protocols have been modified over time. As a consequence, the prognostic factors currently accepted are unsatisfactory[5].

The significance of tumor grade is not always accepted, probably due to varying definitions of anaplasia[6], to discrepancies among pathologists[7], and to the fact that histological features of anaplasia seem to be unrelated to the biological behavior of ependymomas[8]. Another confounding factor is that most series do not distinguish cases with malignant ependymoma from those with ependymoblastoma, which have worse prognoses and distinct classification.

A direct correlation between age and better prognostic was suggested. The small number of cases, the different definitions of pediatric age among series (ranging from 12 to 20 years), and also, the heterogeneity of histological grade and tumor location have not allowed to draw definite conclusions. Ependymomas are rare in adults. Adults present better prognosis and the 5-year survival is about 90%, while in the pediatric population it is around 60%. Overall, the younger the child the worse the prognoses[8]. However, no correlation was observed between age and survival in our series.

The prognostic role of tumor location is also controversial. Intramedullary lesions present more favorable prognosis but the intracranial tumors have uncertain prognoses. Some authors concluded that there was no relationship between prognosis and location, while others concluded that supratentorial lesions indicated worse prognosis due to their infiltrative characteristics in brain parenchyma, hindering total resection[9,10]. Furthermore, infratentorial tumors present a mitotic activity lower than supratentorial tumors[11]. Some authors observed a worse prognosis for ependymoma arising from posterior fossa, which occurs in younger patients and generally invades the brainstem, the floor of fourth ventricle, the cerebellopontine angle and the cranial nerves, making it difficult for a complete resection[9,11]. In this series, no correlation was noticed between the tumor location and the prognosis (correlation with recurrence, p=0.814; correlation with death, p=0.147), although it was observed that gross total resection was more statistically significant in the supratentorial tumors than in the infratentorial ones (83.3% × 31.5%; p=0.01).

The degree of resection was considered an independent prognostic factor; the complete resection presented better 5-year survival than subtotal removal or biopsy[12,13]. In some cases, the benefit of complete resection was limited to low-grade tumors[14]. However, some authors failed to find a correlation between improved survival and the extent of resection[15-17]. The lack of evidence for the impact of surgery on survival could be related to the unreliability of subjective assessment of the degree of surgical ablation, that is, when the degree of resection is not evaluated by postoperative imaging. It was proved that the surgeon evaluated the degree of resection in a different way than that observed in the postoperative imaging in 32% cases[18]. The degree of resection, assessed by postoperative imaging, has been related with an improved follow-up in 5-year survival[18]. In the present series no significant correlation was identified between the degree of resection and improvement in follow-up, such as longer survival or lower recurrence of tumors.

The impact of postoperative radiotherapy in the treatment of these patients was not totally supported due to the absence of controlled and randomized studies. Although data is lacking, there is consensus that postoperative radiotherapy should integrate the standard treatment in the majority of the cases since failure of local control of tumor growth is still the most significant factor contributing to recurrence and poor survival. The option to follow-up patients until there are symptoms of disease progression may be adopted, since late side effects are one of the main complications among long-term survivors. Craniospinal irradiation should be restricted to patients with evidence of cranio-spinal seeding. In this series, postoperative radiotherapy was indicated in subtotal resections or recurrence. In three high-grade tumor cases,

postoperative radiotherapy was indicated although gross total resection was achieved (these cases did not recur).

Intramedullary ependymomas present different prognosis from intracranial tumors. The strongest predictor of post-operative functional outcome is pre-operative functional ability. The aim of surgery is to preserve rather than restore neurological function. The morbidity and mortality are directly related with postoperative deficits, while postoperative deficits correlate with the pre-operative status and the tumor location. The tumor growth is generally slow; outcome and the risk of recurrence depend on the degree of resection in the first surgery[4]. The postoperative radiotherapy is unnecessary when the resection is complete. When resection is incomplete the need of radiotherapy is difficult to interpret, because studies contemplate small series with limited follow-up usually with no control groups[19]. In this series the radiotherapy was indicated only when dissemination was evident and in a case which recurrence was premature (three months after the first surgery). Significant correlation was not observed between the lesion location and survival or the degree of resection (p=0.295 and p=0.362, respectively).

In conclusion, the study of ependymomas is of great interest. Many studies have been published throughout the years; however, handling these patients is still controversial. Surgery alone or combinations of resection with chemotherapy and radiotherapy have been proposed as forms of treatment. The absence of standard treatment and randomized studies hindered the establishment of the best treatment strategy[20]. Although the surgery has a well established role, adjuvant treatment procedures are still uncertain.

In the presented series, the degree of resection was connected with the intracranial tumor location with statistically significant correlation, although this finding was not a predictor for recurrence. The clinical data study of intramedullary ependymoma patients did not allow defining characteristics of survival and probability of recurrence.

It is necessary to understand better the molecular biology of ependymomas to improve the evaluation of the treatment and the outcome of patients.

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