The Outcomes of Treatment of Cauda Equina Ependymomas in Adults


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Ependymoma is a rare tumor that accounts for about 4% of all central nervous system tumors. Ependymomas typically have the intramedullary localization; however, the tumor is sometimes localized outside of the spinal cord, in the cauda equina root region.

Objective. The objective of the study was to analyze the outcomes of treatment in patients diagnosed with extramedullary ependymoma. Material and Methods. Fifty patients (23 males and 27 females aged 18—76 years, mean age of 38.7 years) with ependymoma of the cauda equina region were operated on at the 10th Department of the Burdenko Neurosurgical Institute between January 2009 and December 2013. Thirty-six patients were newly diagnosed with tumors. Fourteen patients were admitted to the Burdenko Neurosurgical Institute with recurrent tumor or continued tumor growth. The patients were subdivided into two groups according to this criterion. The outcomes of treatment were evaluated using the Frankel, Karnofsky, and VAS scales. Criteria (scale) proposed by Kawabata et al. were used to assess the long-term outcomes of surgical treatment. Tumor growth was monitored by contrast-enhanced MRI.

Results. Tumors were divided into two subtypes: encapsulated and infiltrative. Subtotal resection of ependymomas was performed in 5 patients; continued growth of ependymoma was observed in 3 patients. According to the evaluation performed using the scales, positive outcomes were achieved in both groups. According to the criteria of Kawabata et al., the patients were distributed as follows: in group 1, good outcome (class 1) was observed in 26 (72%) patients, satisfactory outcome (class 2) in 8 (22.5%) patients, and equivocal outcome (class 3) in 2 (5.5%) patients. A number of patients received radiotherapy as a component of combination treatment. Tumor growth stabilization was achieved.

Conclusions. Microsurgical intervention is obligatory, since it has a positive effect on outcomes of surgical treatment of intradural extramedullary tumors, in particular ependymomas of the cauda equina region. The treatment efficacy decreases for the infiltrative pattern of tumor growth. Radiation therapy should be used in the case of continued tumor growth or intentionally subtotal tumor resection.

Keywords: intradural extramedullary tumor, cauda equina tumor, myxopapillary ependymoma, Frankel, Karnofsky, VAS.

According to the 2007 WHO Classification of Tumors of the Central Nervous System [1], ependymal tumors include the following types: cellular, papillary, clear cell, tanycytic and anaplastic ependymomas, subependymoma, and myxopapillary ependymoma. The latter is the most common histological type (Fig. 1).

From the topographic anatomy standpoint, ependymomas of the terminal filament are intradural extramedullary spinal tumors of the neuroectodermal origin. Currently, with the advent of the microsurgical technique, resection of extramedullary tumors is not a problem for the neurosurgeon. However, according to the experience of the Spinal Department of the Burdenko Neurosurgical Institute, application of patients with relapses and continued tumor growth creates a complex situation in choosing the tactics of treatment and in understanding disease diagnosis. The purpose of this study was to investigate the early and long-term outcomes of treatment of patients diagnosed with extramedullary ependymoma localized in the cauda equina region.

Material and Methods

A total of 197 patients with the histologically verified diagnosis of spinal cord ependymoma underwent surgical treatment at the Spinal Department of the Burdenko Neurosurgical Institute from January 2009 to December 2013. Of them, an intradural extramedullary tumor was diagnosed in 50 patients. Our observation group included 23 males and 27 females aged 18—76 years (mean age of 38.7 years) with terminal filament ependymomas localized in the cauda equina roots. Despite the fact that the study included patients who underwent treatment during 2009—2013, the follow-up period ranged from 6 months to 25 years (mean of 52.2 months), because this period was calculated since the first surgery listed in the past medical history. All patients were divided into two groups. Group 1 included 36 patients with newly diagnosed ependymomas of the cauda equina. Group 2 was comprised of 14 patients who were previously operated on for ependymoma of the cauda equina and had either recurrent tumor or continued tumor growth. 4 patients had repetitive surgeries; 3 patients underwent subtotal resection at the place of residence; and 2 patients underwent an open biopsy of the tumor.

In 26 cases, ependymomas had the expansive growth pattern and macroscopically appeared as a round or elongated node coated with a dense sac (Fig. 2).

In 24 cases, the tumor had the infiltrative growth pattern, had no sac, and was tightly adjoining to the cauda equina roots (Fig. 3) and to the medullary cone (9 cases).
For simplicity, the term “infiltrative” tumor was used with respect to ependymomas without sac and tightly adjoining to the cauda equina roots.

The mean length of tumors in spinal segments was 2 segments (1 to 5) in group 1 and 4.85 segments in group 2. Ependymomas were typically localized at the L2—L3 level. The disease duration from the onset of symptoms till reference to the neurosurgeon ranged from several months to 14 years, with 31 months, on average, being spent before surgical intervention.

Among the main symptoms, local pain syndrome was observed in all patients and was the chief complaint. Sensory disorders of varying intensity were detected in 16 patients. Paraparesis was observed in 12 patients only. Pelvic dysfunctions were observed in 18 patients. Of them, 12 patients had ischuria, and 6 patients suffered stool retention and enuresis. Ischuria was caused by compression of the medullary cone in 4 cases and by compression of the cauda equina roots in the other cases. Along with pain syndrome, erectile dysfunction was the chief complaint and disease presentation in 5 male patients. The tumor had the infiltrative growth pattern in 13 patients with pelvic dysfunction.

Presurgical examination of the patient included evaluation by a departmental neurosurgeon and neurologist and contrast-enhanced MRI (see Fig. 2 and 3). Patients with newly diagnosed tumors underwent surgery using either laminectomy or hemilaminectomy, which were sufficient to visualize the tumor poles, followed by microsurgical resection. Given the two different patterns of tumor growth (encapsulated and infiltrative), various resection techniques were applied. En block resection was used for encapsulated tumors (Fig. 4).

Ependymomas with the infiltrating growth pattern and without a sac were resected by intratumoral decompression and morcellation, i.e. by reducing the tumor volume using an ultrasonic aspirator and microsurgical instruments, followed by resecting the tumor in several fragments (Fig. 5).

In 11 cases, the dura mater was thinned and had a defect. After tumor resection, there arose the need for enthesis using synthetic glue materials (Gore Preclude, TachoComb, Tissucol, or Resodura). The enthesis efficacy was achieved in 10 cases. In one case, there was the necessity in revision of a surgical wound to remove a cerebrospinal fluid (CSF) cyst and to close a CSF fistula of the dura mater. In the second case, liquorrhea was resolved by draining the cerebrospinal fluid via a lumbar drainage and repeated wound punctures.

In 6 cases of subtotal tumor removal, radiation therapy was used; 3 patients underwent a course of conventional radiation therapy at the place of residence. The mean exposure dose for the longitudinal axis of the spinal canal was 50.4 Gy. Three patients underwent stereotactic radiotherapy in the hypofractionation regimen using the CyberKnife system at the Burdenko Neurosurgical Institute. The hypofractionation regimen involved 14—16 Gy delivered in 3—5 fractions (Fig. 6).
Results

A postoperative examination of the patient included evaluation by a departmental neurosurgeon and neurologist as well as contrast-enhanced MRI 3 months and 1 and 3 years after surgery. In the long-term postoperative period, an analysis was conducted based on the data of outpatient observation; MRI was performed when needed.

Only 1 (2.7%) ependymoma relapse with infiltrative growth was detected in group 1. The relapse was detected due to the clinical presentation 5 years after surgery.

In group 2, subtotal resection of ependymomas was performed in 5 (35.7%) cases. Continued tumor growth was observed in 2 (14%) patients during follow-up.

According to the MRI data, no dynamics of tumor growth was detected in 3 patients. Neurological symptoms emerged and progressed in 2 (14%) cases (complaints appeared 12 months after reoperation in the first case and after 36 months in the second case).

Radiation therapy provided a positive outcome in 5 patients in the form of tumor growth stabilization and pain reduction by more than 3 points on the VAS scale during a follow-up period of 12 to 28 months. According to the literature [2, 3, 5, 6, 8], conventional therapy has been widely used for ependymoma treatment. Radiation therapy in the postoperative period significantly reduces the tumor growth rate [7]. No stabilization of tumor growth after radiation therapy was observed in 1 case.

Fig. 3. MRI of anaplastic ependymoma of the cauda equina at the T12—L5 level before and after surgery.

Fig. 4. Intraoperative images of encapsulated ependymoma.

1 — cauda equina roots; 2 — tumor; 3 — terminal filament.
Treatment outcomes were determined using the Frankel classification for assessment of the neurological status, Karnofsky scale of the life quality, and visual analogue scale of the pain syndrome intensity. Also, tumor growth or tumor relapse was controlled using the MRI data.

In group 1, the following grades were obtained according to the Frankel classification (Table 1): grade C (2 patients), grade D (26 patients), and grade E (8 patients). According to the Frankel grading system, the following grades were detected in group 2: grade C (4 patients) and grade D (10 patients). According to the Karnofsky scale, the distribution of patients in group 1 was as follows: 4 patients had a score of 60, 30 patients had a score of 70, and 2 patients had a score of 90. In group 2, the results were as follows: 9 patients had a score of 60, and 5 patients had a score of 70.

The assessment of pain syndrome on the VAS pain scale was performed before surgery and in the long-term postoperative period (Fig. 7). Clear predominance of severe pain syndrome was observed in group 1 where 29 (80%) patients had more than 7 points.

In the long-term follow-up period, the following outcomes were achieved in group 1: on the Frankel scale (see Table 1), 18 (50%) patients were upgraded; 8 (22.5%) patients had the same grade E; 8 (22.5%) patients had the same grade D and C (7 and 1 patients, respectively); and 2 (5.5%) patients were downgraded.

In group 2 of patients who underwent reoperation, the following results were achieved (see Table 1): 3 (21.4%) patients were upgraded, of whom 2 patients were upgraded from C to D and 1 patient was upgraded from D to E; 10 (64.2%) patients had the same grade, namely 2 patients with grade C and 8 patients with grade D; and only 1 (7%) patient from D was downgraded.

In the long-term follow-up period, the assessment of patients in group 1 according to the Karnofsky scale showed that an improvement in the quality of life (increasing the score) was observed in 32 (89%) patients; no change in the score was in 2 patients (5.5%); and the score was decreased in 2 patients (5.5%).

In group 2, the quality of life was improved in 8 (57%) patients, remained the same in 4 (28.5%) patients, and worsened in 2 (14.5%) patients only.

According to the VAS scale (see Fig. 7), regression of pain syndrome by more than 3 points on the analogue scale was considered as a positive outcome. In group 1, complete regression of pain syndrome was observed in 26 (72%) patients; a decrease in pain was noted in 6 (16.6%) patients. Three (8.3%) patients had a decrease in the pain...
syndrome intensity, but by less than 3 points. Pain aggravated in 1 patient. In group 2, regression of pain syndrome occurred in 10 (72%) patients, and poor outcomes were observed in 4 (28%) patients: 2 (14%) had complains of aggravated pain, and the pain reduced only by 2 points in the other 2 (14%) patients.

The long-term outcomes were evaluated (Table 2) using three classes of the Kawabata et al. scale (criteria).

According to the criteria of Kawabata et al., patients were distributed as follows: group 1, good outcome (class 1) was observed in 26 (72%) patients, satisfactory outcome (class 2) in 8 (22.5%), and equivocal outcome (class 3) in 2 (5.5%) patients only. In the postoperative period, the equivocal outcome in one of the two patients resulted from aggravated local pain in the lumbar spine. These complaints were associated with a concomitant degenerative spine disease. After surgery, the second patient with the infiltrative growth pattern of ependymoma adjoining to the medullary cone developed sensory disorders and pelvic dysfunctions. Both these patients received conventional radiation therapy that improved their condition. In the first case, the pain syndrome regressed. Unfortunately, in the second patient, no sensory disorder regression was observed on the background of recovery of pelvic organ functions.

In group 2, the results were as follows: good outcome was observed in 3 (21.4%) patients, satisfactory outcome in 9 (64.4%) patients, and equivocal in 2 (14.2%) patients. In 1 patient, worsening of the neurological symptoms occurred after removal of large recurrent ependymoma with a sacral ulcer due to the tumor. Also, the equivocal outcome in 2 patients was associated with continued...
Table 1. Assessment of patients’ neurological status on the Frankel scale

<table>
<thead>
<tr>
<th>Before surgery</th>
<th>After surgery</th>
<th>Overall</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
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<tr>
<td>Group 1</td>
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<td>A</td>
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<td>C</td>
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<td>Total</td>
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<tr>
<td>Total</td>
<td>14</td>
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</table>

Footnote. A—E are the types of neurological spinal disorders.

Table 2. Criteria for assessment of treatment outcomes (Kawabata et al.)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Criterion</th>
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<tr>
<td>Good (class 1)</td>
<td>No complaints and pathological symptoms, normal results of objective examination, significant improvement, no disabling dysfunction</td>
</tr>
<tr>
<td>Satisfactory (class 2)</td>
<td>Minor complaints, some residual symptoms, and minimal objective signs</td>
</tr>
<tr>
<td>Equivocal (class 3)</td>
<td>Retained complaints, no positive dynamics, or worsening</td>
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Discussion

Tumors of the cauda equina occur very rarely compared to other neurosurgical pathologies. Ependymomas of this localization are much less common. The series of examined patients that is described in this article is the largest one in the CIS countries and is one of the largest series in the world. For example, 62 patients were operated on at the Romodanov Institute of Neurosurgery (Kiev, Ukraine) for 20 years (from 1988 to 2007) [3].

In most cases, extramedullary ependymoma do not cause motor deficits in the absence of medullary cone compression. Based on analysis of a group of patients with ependymomas of the cauda equina, L. Meneses et al. [4] divided the symptoms into local pain (31.25%), radicular pain (56.25%), and paraparesis (12.5%). A decrease in the motor function was observed only in every 10th—12th patient in the series and was accompanied by urination and defecation disorders and sexual dysfunction. In this case, severe local and radicular pain syndromes as well as sensory disorders caused intense discomfort and were the main cause of disability and reference to a doctor.

The precursory symptoms of the disease usually include unilateral sensory disorders in certain sensory areas. While progressively spreading from the tumor localization level down to the feet, the sensory disorders become bilateral. This phenomenon progresses along with an increase in the tumor size.

Urination disorder, like sexual dysfunction, develops in a small number of patients. The development of these symptoms is associated with medullary cone compression. The medullary cone includes sacral plexus segments that are responsible for the pelvic organ function. In our series of observations, only 4 of 18 patients with the pelvic organ dysfunction had tumors at the medullary cone level. The remaining 14 patients with the pelvic organ dysfunction had the tumor localized distal to the cone and had, to our opinion, more pronounced symptoms. For example, the dysfunction was accompanied by enuresis and stool retention in 6 cases. Unfortunately, no regression of this disease manifestation occurred during the postoperative follow-up after tumor resection, even on the background of specific therapy. This is likely related to microcirculation failure in the cauda equina roots that resulted from long-lasting compression by the tumor; however, we could not find confirmation of this fact in the literature. Remarkably, the tumor had the
infiltrative growth pattern in most cases (13 patients) of pelvic organ dysfunction.

P. Sonneland et al. [2] and E.I. Slyn'ko and A.G. Karleychuk [3] in their series divided tumors into two patterns of growth (infiltrative and encapsulated) affecting treatment outcomes. Certainly, this was not true infiltrative growth but exophytic one, since ependymomas of the cauda equina do not grow into adjacent structures. In our own practice, we have often observed the inclusion of the cauda equina roots in the tumor sac. Frequently, these ependymomas can reach a giant size. Two patients in our series were detected with giant ependymomas. The tumors of the cauda equina were large in size and extended over more than 7 spinal segments (T10—S3). These tumors compressed the medullary cone and occupied the whole space inside the sac ending in the sacrum region. In these cases, destruction of the bone tissue was observed; the tumor stretched the presacral fascia and penetrated to the pelvic region (Fig. 8).

We analyzed the treatment outcomes of large international series of patients. For example, complete resection of ependymomas was achieved in 80% of cases in a series presented by E. Kucia [5] and in 73.4% of cases in a series presented by M. Nakamura [6]. According to P. Sonneland et al. [2], radical resection was achieved only in 59% of patients. In a series of patients operated on at the Burdenko Neurosurgical Institute, total tumor resection was achieved in 33 (91%) cases in group 1 and in 9 (64%) cases in group 2. Undoubtedly, these data indicate that there are a large number of unsatisfactory outcomes in reoperated patients.

Resection of the tumor with the infiltrating growth pattern that was tightly adherent to the cauda equina roots was a complex problem. Total resection of ependymoma of this type was performed with extreme caution. The basic principle of surgery was the maximal safe resection [2, 5, 9]. During surgery, it was necessary to correlate the radicalness of tumor resection and the risk of neurological deficit in the postoperative period. We used neurophysiological monitoring with analysis of evoked motor and sensory potentials in order to prevent neurological complications. M. Meneses et al. in their study also emphasized the need for neurophysiological monitoring.

Recurrent tumors were observed in 19% of cases, according to P. Sonneland et al. [2]; in 10% of cases, according to E. Kucia et al. [5]; and in 7.4% of cases, according to E.I. Slyn'ko and A.G. Karleychuk [3]. No relapse was revealed by M. Meneses et al. [4] in a series of 16 patients with a follow-up period ranging from 2 to 84 months.

According to the 2013 National Comprehensive Cancer Network (NCCN) guideline for the management of patients with primary tumors of the spinal cord [9], which was developed in the USA, it is recommended to perform the maximal safe resection with subsequent follow-up and regular MRI. Repeated surgical
intervention or radiation therapy is recommended if continued tumor growth or relapse is detected. The tactics for treatment and follow-up of patients with extramedullary tumors of the spinal cord was developed at the Spinal Department of the Burdenko Neurosurgical Institute based on the acquired experience (see Diagram).

The patient is subjected to surgical intervention (tumor resection) when a radiographically verified intradural tumor, ependymoma of the cauda equina, is detected by contrast-enhanced MRI. Depending on the radicalness of surgery and histological diagnosis, further treatment tactics for the patient is planned. In the case of total tumor resection, the patient is recommended to have contrast-enhanced MRI 3, 12, 36, and 60 months after surgery (regardless of the tumor growth pattern) with subsequent evaluation by the neurosurgeon. In the case of subtotal tumor resection or a high risk for relapse, the patient consults the radiologist and, if necessary, undergoes radiation therapy. Patients who are detected with a recurrent tumor during follow-up and lack progression of neurological symptoms are recommended to have stereotactic radiotherapy for the tumor. Reoperation is performed in the case of aggravation of the neurological symptoms associated with motor or sensory deficit; radiation therapy is not the method of choice in this case.

Neither chemotherapy nor targeted therapy was used for treatment of patients in our series. However, chemotherapy for treatment of ependymomas in adult patients is limited and is used if radiotherapy is not effective. Forty-four patients out of 127 patients with anaplastic ependymoma received cisplatin, lomustine, and vincristine in a study by A. Korshunov et al. [10]. According to this study, patients who underwent chemotherapy had better outcomes (extended relapse-free period and stabilization of tumor growth) compared to patients who did not receive chemotherapy (78% vs 48%; $p=0.01$).

Several authors have also noted the efficacy of chemotherapy or targeted therapy in patients with continued growth of grade III ependymoma. For example, N. Fakharai et al. [11] reported a clinical case of the use of imatinib in treatment of a female patient with continued growth of a cauda equina tumor (grade II ependymoma); the patient was followed up for 11 months. A regression of the neurological symptoms and positive dynamics, according to MRI, in the form of a tumor volume reduction were observed. Good outcomes in the form of stabilization of ependymoma growth were achieved by oncologists from the USC Norris Comprehensive Cancer Center (Los Angeles, California, United States) [12]. Ten patients diagnosed with grade III anaplastic ependymoma were involved in the study. They received etoposide therapy (50 mg/m² a day) in 2 cycles of 21 days each with a 14-day interval. Stable, good outcome (stabilization of tumor growth) was achieved in 5 (50%) patients. However, most patients of the study group (9 (90%)) had gastrointestinal and hematopoietic complications.

Fig. 8. MRI and SCT of a 54-year-old male patient K. with recurrent myxopapillary ependymoma at the T12—L1 level. The patient was operated on at the place of residence in 1988 and 1989; he received a course of radiation therapy with the total boost dose of 44 Gy in 1991.
Conclusion

The use of the microsurgical technique in modern neurosurgical practice has resulted in a significant improvement in outcomes of surgical treatment for intradural extramedullary tumors, particularly tumors of the cauda equina. This is largely related to the radicalness of resection of ependymomas in the cauda equina region, with the risk for injury of surrounding structures being relatively low. The maximal radical resection should be followed during tumor resection. If necessary, tumor parts tightly adherent to the cone and cauda equina roots should be left to preserve the nervous tissue function. The use of an ultrasonic aspirator can not ensure radical resection in this situation. At present, with the availability of modern neuroimaging techniques enabling sufficiently correct differential diagnosis, there is no reason for a tumor biopsy. It should be noted that the pattern of tumor spreading or tumor growth largely affects the rate of tumor relapses and the radicalness of their resection. Therefore, the quality of life of patients in the postoperative period is affected as well. Most patients are of working age, but they can not fulfill their duties due to severe pain. Surgical treatment of ependymomas is highly effective in reducing pain after surgery and increasing patients’ quality of life. As the experience has proven, great attention should be paid to control and follow-up of patients in the postoperative period, even after total tumor resection. Timely detection of a recurrent tumor could help to avoid repeated surgical intervention and apply an alternative method of treatment, e.g., radiation therapy. Analysis of the literature demonstrated ambiguous evaluation of the efficacy of radiation therapy for treatment of cauda equina ependymomas. Despite this fact, radiation therapy is the method of choice, and importance of stereotactic radiotherapy is growing.

Given the lack of consensus on the role of chemotherapeutic drugs in treatment of ependymomas in adult patients, we are not in the position to recommend this method. However, this method of treatment is promising for patients with repeatedly occurring recurrent tumors resistant to radiation therapy. Therefore, it is necessary to continue studying biology of ependymoma cells and methods of their drug treatment.

REFERENCES

Ependymomas of the cauda equina of the spinal cord belong to the group of extramedullary tumors. They comprise a separate pathomorphological subgroup of the so-called myxopapillary ependymomas. Interestingly, according to the classification of central nervous system tumors, myxopapillary ependymomas are absolutely benign tumors (grade I), and should have theoretically a better prognosis than intramedullary ependymomas (grade II) in adults. The clinical series of 197 patients presented in the study demonstrates all the difficulties and problems in treatment of invasive ependymomas of the cauda equina. Indeed, for some reason, a number of myxopapillary ependymomas are aggressive. They infiltrate surrounding structures, recur, and form drop metastases. Unfortunately, the authors did not analyze the factors that may affect the “biological behavior” of myxopapillary ependymoma. My own experience shows that the tumor size at the time of surgery is one of these factors, which indirectly reflects the timeliness of diagnosis. For example, the signs of arachnoid infiltration are hardly ever seen for tumors of up to 5 cm in length. Long-term, chronic compression of surrounding neural structures by a tumor leads, for unclear reasons, to infiltration of these structures. The radicalness of the first surgery is another factor. Many times, I have operated patients with a so-called “relapse” that is, in fact, a progression of the residual tumor. In these situations, even repeated surgery may be radical and result in recovery. A more significant and, in fact, unsolvable problem is giant ependymomas (5—7 grades) causing destruction of the dura mater and vertebral bodies. These tumors always infiltrate both the roots, cone, and arachnoid and the dura mater, even destroying the latter and spreading into soft tissues. All patients whom I operated on for these giant tumors had been followed up for a long time by various specialists, sometimes having the MRI proven diagnosis, and had “drifted” to surgery for years (or even decades). These cases are a vivid example of the importance of timely diagnosis and early surgical treatment of ependymomas of the cauda equina. A trivial delay in surgery for a few years transforms a potentially curable condition to incurable one. The role of radiation therapy in the treatment of infiltrative tumors is correctly highlighted by the authors. Meanwhile, I strongly believe that the way to improve outcomes of treatment of myxopapillary ependymomas is timely diagnosis and high quality surgery, but not adjuvant therapy.

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