

Prognostic Factors for Neurological Outcome after Resection of Intramedullary Spinal Cord Ependymoma

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Abstract: Background: Radical resections of spinal ependymomas were made possible by many neurosurgeons with the advantages of electrophysiological spinal cord monitoring. Objective: to clarify the good neurological outcome prognostic factors and survival after surgical excision of spinal ependymomas. **Patients and Method:** The current study enrolled 25 patients with spinal ependymomas. Neurological function and MRI were evaluated preoperatively, at discharge, 6-month and 12-month thereafter. Factors associated with gross-total resection (GTR), progression-free survival (PFS), and long-term neurological improvements were assessed. Results: The mean age was 40 years. All pathological types of ependymomas are included. GTR was achieved in 22 cases (88%). Nine patients (36%) experienced acute neurological decline post-operatively where 7 (77.7%) of them were older and had bad preoperative baseline. In 5 patients (20%) showed tumor progression after 13 months follows up. Tumor histology, the presence of an intraoperatively identified tumor plane and adjuvant radiotherapy correlated with improved PFS. Twenty two patients (88%) maintained neurological improvement after 12 months. The presence of neurological symptoms improvement before discharge was associated with overall good outcome (mean 13 months). **Conclusion:** GTR can be safely achieved in the majority of spinal ependymoma when an intraoperative plane is identified, independent of pathological subtype. The incidence of acute perioperative neurological decline increases with patient age but will improve to baseline in nearly most of patients within 1 month. Long-term improvement in motor, sensory, and bladder dysfunction occurs more frequently in patients with identified surgical plane; therefore a GTR should be attempted for all ependymomas.

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1. Introduction:

Ependymomas represent 4% to 6% of primary central nervous system tumors. One-third of them arise within the spinal cord (intramedullary spinal cord ependymoma (IMSCE)).¹ Ependymomas are unencapsulated glial neoplasms, but the vast majority have benign histological form with little infiltrative and slow biological growth. Generally, Ependymomas are characteristically the most common intramedullary spinal cord neoplasm in the adult and have prolonged average symptom duration more than 2 years, preservation of neurological function in patients with extreme spinal cord compression, and long survival times following various forms of treatment.^{2,3}

More than one half of ependymomas, occur in the lumbar region, specifically the conus medullaris and filum terminale. Typical presentations for these types of tumor include pain, bladder dysfunction, lower-extremity paresthesias and weakness.^{3,4,5}

Total resection in selected patients results in good long-term outcomes; however, subtotal resection can be associated with tumor recurrence,

especially if no adjuvant therapy is administered.⁶ The postoperative radiation therapy is essential and may reduce the incidence of recurrence and improve survival rate. Chemotherapy may also have a potential role in certain progressive tumors, but its role is not clearly defined.^{7,8}

The risk of paralysis after surgery in patients with no or minimal preoperative deficits is 1%, but the risk is much higher in those with more deficits. Many patients may have significant temporary motor deficits especially in tumors that are difficult to remove.^{6,9,10}

The aim of this long-term current study is the clarification of good prognostic factors as regard neurological outcome and survival after surgical excision of spinal ependymomas either total or partial.

2. Patients and Methods:

The current study enrolled 25 consecutive cases with IMSCEs which have been resected between 2005 and 2012. All clinical, radiographic, electrophysiological, operative, and pathological

reports were recorded for all patients. Functional neurological status was classified using the MMS (Modified McCormick Scale) [table 1] and overall improvement or deterioration was identified by either moving up or down one grade of the preoperative status. Improvement or deterioration of the motor function alone was indicated by either increase or decrease of the average MRC grading scale of the lower limb muscle groups bilaterally by 1 point.

The extent of the excision was defined as a GTR (gross total resection) if there was no residual enhancement on postoperative MR imaging; otherwise, the excision was classified as an STR (subtotal resection). Acute post-operative neurological decline was defined as motor weakness more than preoperative baseline status.

Clinical standard follow-up consisted of clinic visits at 1 month, 6 months and then at 12 months thereafter, with documented neurological status (motor, sensory, or urinary) of all patients as whether worsened, improved, or unchanged from preoperative baseline. All patients underwent MRI preoperatively, 1 month postoperatively, and then at 6 months whenever indicated. Electrophysiological evaluation was done before and at 6 ms postoperatively. Time to

tumor progression was defined as time from resection to increased tumor burden on follow-up MRI.

Electrophysiological study: Somatosensory Evoked Potential (SSEP) was completed in 50 lower limbs by stimulating peroneal nerve at the lateral fibular neck. The stimulator cathode was placed 4 cm proximal to the anode lateral to the fibular neck. Pick up active electrode was placed over Cz' (2 cm posterior to Cz) with the reference electrode placed over Fpz' (2 cm behind Fp). The ground electrode was placed on the back of the upper thigh. The equipment was set at the standardized values. Average N1 peak latency values of the 2 lower limbs in each patient was used for interpretation

Surgical microscope resection was done in all cases. Laminectomy was done at the width of the spine over the length of tumor. Outside-in resection technique was used for small to moderately sized ependymomas when identification of tumor-spinal cord transition plane was clear. Inside-out resection technique was utilized in large ependymomas until reaching a transition to spinal cord where no residual left.

Table 1: Clinical/functional classification scheme*

Grade	Definition
I	Neurologically normal; mild focal deficit not significantly affecting function of involved limb; mild spasticity or reflex abnormality; normal gait
II	Presence of sensorimotor deficit affecting function of involved limb; mild to moderate gait difficulty; severe pain or dysesthetic syndrome impairing patient's quality of life; still functions and ambulates independently
III	More severe neurological deficit; requires cane/brace for ambulation or significant bilateral upper-extremity impairment; may or may not function independently
IV	Severe deficit; requires wheelchair or cane/brace with bilateral upper-extremity impairment; usually not independent

*Reproduced from McCormick PC, Torres R, Post KD. Intramedullary ependymoma of the spinal cord. J Neurosurg. 1990;72:523-532.

Adjuvant radiotherapy was received in group of patients who had been followed for long period up to 5 years by radiotherapist, the dose of radiotherapy ranged between 45 and 50 Gy (Daily fractions 1.8-Gy) using linear accelerator 6 MV photon.PFS was calculated from the date of start treatment to the date of documented progression. Predictors that include age, duration of preoperative symptoms, tumor size (number of spinal levels), location, presence of intraoperative plane, tumor histology and presence of a syrinx, were tested for association with GTR, acute

neurological decline and neurological outcome (Fig. 2).

Statistical analysis: The data were coded and entered into a computer using SPSS version 15.0. Survival functions (PFS) were estimated using the Kaplan-Meier test.

3.Results:

Thirteen patients (52%) presented with motor weakness, seven (28%) with sensory symptoms, and 5 (20%) with bladder dysfunction. Fourteen tumors (56%) involved the lumbar spine, 6 (24%) involved

the conus medullaris and 5 (2%) in cervicothoracic cord. In 22 cases (88%) there was a clearly identifiable tumor plane observed during resection in non-infiltrative ependymomas (Fig. 1) (Table 2).

Perioperative morbidity included 2 cases (8%) of surgical site infection, 1 (4%) CSF leaks, 1 (4%) deep vein thromboses, 1 (4%) epidural spinal

hematoma, and 18 (72%) patients were transferred to outpatient rehabilitation. In the minority of cases (6 cases [24%]), surgery was used alone without adjuvant radiotherapy. The median PFS in patients received adjuvant radiotherapy was 63 months (95% CI 56.31-67.68) and the 5 years PFS was 68.4%.

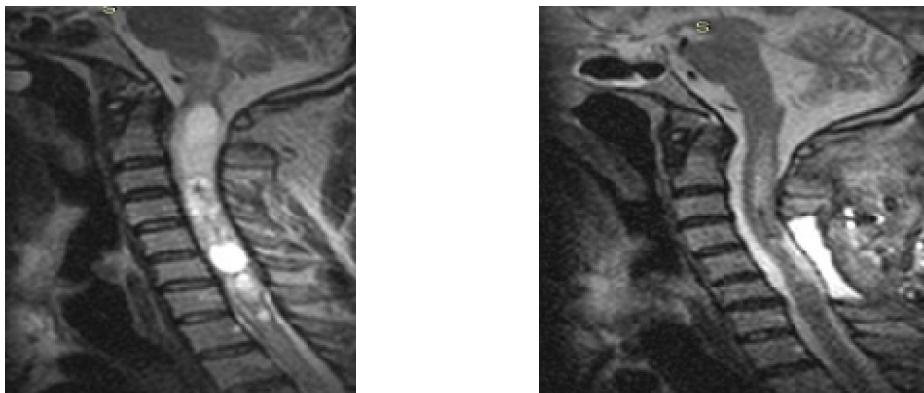


Fig. 1: Sagittal T2-weighted MRI pre and postoperative images through cervical spinal cord ependymoma show hyperintense round lesion image (left) and postoperative with mild cord atrophy (right).

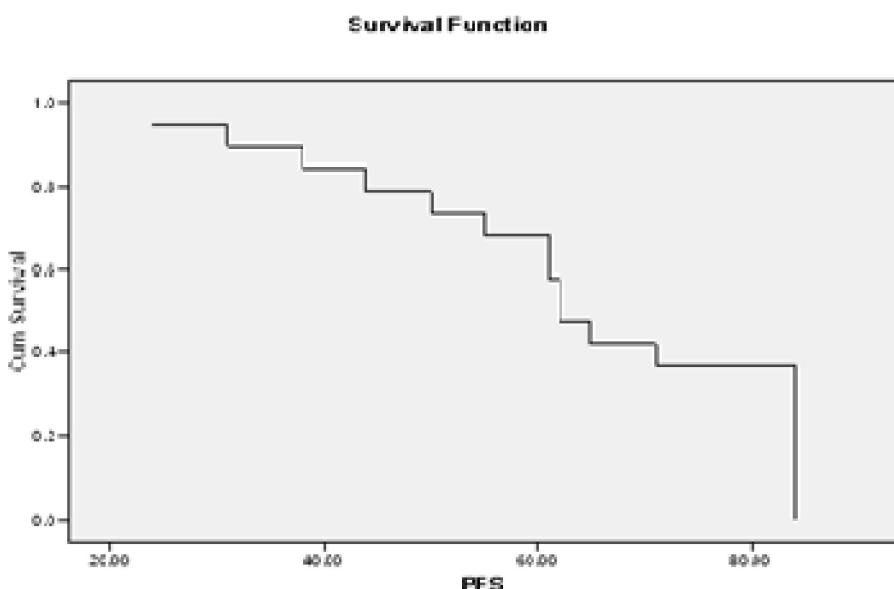


Fig. 2: PFS among all studied patients received radiotherapy.

Short-Term Neurological Outcome

Acute postoperative neurological decline occurred in 9 patients (36%), 7 (77.7%) of them returned to their preoperative baseline by one month. The incidence of acute decline was not different among tumor pathological subtypes but was common among older patients who showed bad motor recovery (>50 years). Neither GTR nor the presence

of an intra-operative tumor plane was associated with acute decline.

GTR was achieved in 22 patients (88%). the presence of a clear intraoperative tumor plane and decreasing tumor size were associated with an increased likelihood of a GTR.

Tumor progression developed in 3 patients (12%) at a median of 10 months postoperatively.

Progression-free survival correlated closely with tumor histology. The presence of an identifiable tumor plane was associated with improved PFS. A GTR, compared with STR, was associated with improved PFS.

Long-Term Neurological Outcome (≥ 1 year post-operatively)

Following a period of 12 months post-surgery, in the patients who had presented with sensory, motor, or urinary dysfunction, or a combination of these, dysesthetic symptoms improved to minimal or none in 4 out of 7(57%), near-full strength in 11 out of 13 (84.6%), and bladder dysfunction improved to urine continence in 3 out of 5 (60%). The median MMS score at last follow-up was similar to the

median preoperative MMS score. Identification of a tumor plane at the time of resection and rapid improvement were associated with an increased likelihood of long-term overall neurological outcome.

SSEP: 24 (96%) out of 25 patients had abnormal peroneal SSEP where 10 (44%) showed neglect response and 7 of them regained a postoperative recordable response at 6 months point. 14 (56%) out of 24 patients revealed prolonged mean N1 latency (32.5 ± 2.4 ms) pre-operatively and all showed an improvement of the mean N1 SSEP latency (29.1 ± 1.4 vs 32.5 ± 2.4 ms) at 6 months point postoperatively ($p=0.07$).

Table 2: Patient characteristics

Clinical/ Radiographic Variables	No. of Patients/ Value (%)
Demographic data	
Mean age (yrs)	41.5±5.2
Male	15 (60)
Female	10(40)
Clinical parameters	
Preop motor weakness	13 (52)
Preop sensory dysesthesias/paresthesias	7 (28)
Preop sphincteric dysfunction	5 (2)
Median duration of symptoms (month)	4
Median preop MMS score (Grade 1–5)	2
Radiographic parameters	
Mean no. of spinal levels	3
Cervico-thoracic region	5(20)
Lumbar segment region	14 (56)
Conus area	6 (24)
Tumor-associated syrinx	9 (36)
Periop parameters	
Intraop identifiable transition (plane)	22 (88)
GTR	22 (88)
Acute postop neurological decline	9 (36)
Op site infection	2 (8)
CSF leak	4(1)
Deep vein thrombosis	4(1)
Epidural hematoma	4(1)
Discharge to rehabilitation facility	18 (72)
Histology	
Subependymoma (WHO) grade I	1(4)
Myxopapillary ependymomas WHO grade I	5(20)
Ependymomas WHO grade II	17(68)
Anaplastic ependymoma WHO grade III	2(8)

4. Discussion:

D. Gavin et al., stated that longer symptom duration prior to treatment is associated with poorer functional outcome: therefore early diagnosis and treatment carry better prognosis.⁷ In the current study GTR was achieved in the majority of cases but was dependent on tumor size and the presence/absence of intraoperative tumor planes. Acute neurological decline occurred in nearly one-third of patients (36%), but the rest of patients (77.7%) returned to baseline within 1 month of surgery. In the great preponderance of patients, preoperative neurological dysfunction improved and was maintained by the last follow-up. This long-term improvement was frequently observed in patients with rapid improvement at discharge or in those with clear tumor planes. It is concurrent with Giannina and Garcés-Ambrossi study.¹¹

Tissue histology determined the progression-free survival though it was highly variable. Also the presence of identifiable tumor planes carried positive prognostic significance regardless of tumor type. As observed in their series, IMSCT respectability and long-term prognosis were most closely correlated with tumor histology (Table 2).¹¹

Schwartz et al., and Chang et al., concluded that in the surgical treatment of spinal cord ependymoma, preoperative functional status and the extent of removal were the significant prognostic factors influencing postoperative outcome. In the aspect of disease progression, the only statistically significant factor by multivariate analysis was the surgical extent of removal.^{12, 13} An incomplete resection proved the only independent predictor of progression-free survival (Fig. 2).¹⁴

In the current study, the smaller size of tumors (defined by number of spinal levels) was correlated with increased odds that a GTR would be achieved (e.g. en bloc resection when tumor planes were identifiable). This avoids the risk of cord traction and manipulation in cases of larger tumors. GTR has been associated with improved prognosis for low-grade intramedullary tumors such as ependymoma and hemangioblastoma.^{15, 16, 17} Most series have studied the association between GTR and long-term outcomes, rather than that between GTR and tumor size.¹⁸⁻²⁰

The association of GTR with an intraoperatively identified plane of tumor resection is not surprising; a plane highlights the safe margin for aggressive resection and simplifies the post-resection search for residual tumor. In another series, it concluded that the decreased tumor size was associated with an increased GTR achievement where tumors were more

amenable to en bloc resection when tumor planes were identifiable (Fig.1).¹⁰

Preoperative functional status was a significant prognostic factors influencing postoperative outcome where the incidence of acute decline was in 9 patients (36%) which is little higher than the published rate of ~ 20% and this might be related to relatively limited number of the studied patients.¹³ Increasing age was the only factor independently associated with acute postsurgical neurological decline. Older patients may have less pliability after surgical insult because older patients may not compensate for the microcirculatory instability experienced intraoperatively.

Interestingly, about three quarter of patients (77.7%) recover their preoperative baseline strength within 1 month; this may be related to the use aggressive postoperative rehabilitation and steroids for postoperative edema. Transient motor decline is poorly studied, however other studies report up to two-thirds of patients regaining strength ~6 weeks after resection.¹⁶

In one study, Forty-nine of 57 patients (86%) had stable or improved McCormick grades directly after surgery. A permanent decrease in the McCormick grade was seen in 4 (7%) patients. Multivariate logistic regression revealed only the preoperative neurological status of the patient as an independent predictor of functional outcome.¹⁴

Long term neurological improvement occurred in the majority of patients as regard their motor deficits (93%) and the bladder control (72%) while the dysesthetic symptoms improved (49%) after one year of surgery and all of them were linked to the presence of an intraoperative tumor plane. This is not surprising, as ependymoma with clear planes between the tumor and the spinal cord may allow for resection without invasion into functioning spinal cord tissue. In infiltrating lesions, the transition from tumor to functional spinal cord tracts is not clear, increasing the risk of excessive resection with functional consequence. Early improvement in baseline deficits before discharge identified those patients who are better responders to surgery (Fig. 2).

In the present study, 19 patients received adjuvant radiotherapy, the median PFS was 63 month and the 5-year PFS was 68.4%, this results are comparable to Benesch et al., who reported 5-year PFS 72.3% for patients underwent GTR and 57.1% for patients with less than GTR and Pica et al., who reported 74.8% 5-year PFS concluding that RT improved time to progression.^{21, 22}

Conclusion:

Gross-total resection can be safely obtained in the majority of spinal ependymoma if an intraoperative plane of tumor resection is identified. The incidence of acute perioperative neurological decline increases with patient age, but will improve to baseline in nearly three quarter of these patients within 1 month. Long-term improvement in motor, sensory, and bladder dysfunction may be achieved in the majority of patients; considering that patients with identifiable surgical planes are most likely to experience long-term sustained neurological improvement. For improved PFS, GTR should be practiced in all cases of ependymoma. The presence of identifiable tumor planes carried positive prognostic significance regardless of tumor subtype and suggests that this gross tumor characteristic may offer valuable prognostic information regarding biological aggressiveness and subsequent tumor recurrence. GTR remain the main curative treatment of ependymoma, however adjuvant radiotherapy improve PFS.

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