

Spinal cord ependymoma: a review of the literature and case series of ten patients

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Abstract Spinal cord ependymoma (SCE) is a rare tumor that is most commonly low-grade. Complete surgical resection has been established as first-line treatment and can be curative. However, SCEs tend to recur when complete tumor resection is not possible. Evidence supporting the use of adjuvant radiation and chemotherapy is not definitive. We review the most recent literature on SCE covering a comprehensive range of topics spanning the biology, presentation, clinical management, and outcomes. In addition, we present a case series of ten SCE patients with the goal of contributing to existing knowledge of this rare disease.

Keywords Spinal cord · Ependymoma · Tumor · Review · Case series

Clinical presentation and diagnosis

In the United States, 1000–2000 adults are diagnosed with spinal or intracranial ependymoma each year. In adults, 75 % occur in the spinal canal, making up 25 % of intramedullary spinal cord tumors and 2 % of primary central

nervous system (CNS) malignancies [1]. Patients are usually 30–40 years old, men and women affected equally.

Spinal cord ependymoma (SCE) patients typically present with nonspecific symptoms progressing over years prior to diagnosis, although rare instances of intratumoral hemorrhage can provoke acute deterioration [2–4]. Common symptoms include back pain, spasticity in the lower extremities, gait ataxia, sensory loss, and paresthesias. Cervical tumors can present upper or lower extremity symptoms if they affect the corticospinal tract or dorsal columns, respectively. Lumbar tumors may cause incontinence, radicular back and leg pain, and even asymmetric weakness if the tumor causes significant mass effect in more advanced disease.

The WHO histologic subtypes of ependymoma are classified into three grades based on degree of malignancy seen on microscopy [5]. Myxopapillary ependymoma and subependymoma are grade I lesions, the most benign in histologic appearance. Grade II lesions include classic, cellular, papillary, clear cell, and tanycytic subtypes, grouped together for their lack of anaplastic features and similar biologic behavior [6]. Anaplastic ependymomas are grade III, and correspondingly have the most malignant behavior. The grades differ in their most likely locations within the spinal cord, ease of resection, and tendency to recur.

Grade II “classic” ependymoma comprises 55–75 % of lesions in the spinal cord [7, 8], most commonly occurring in the cervical or thoracic region, rarely in the lumbar cord [9]. Grade II spinal cord ependymomas are typically intraparenchymal and often cystic (one series reported 58 % were associated with a syrinx) [9]. Characteristic histologic features include pseudorosettes and “true” or “ependymal” rosettes, which are present in approximately 80 % [10] and 10 % of ependymal tumors, respectively

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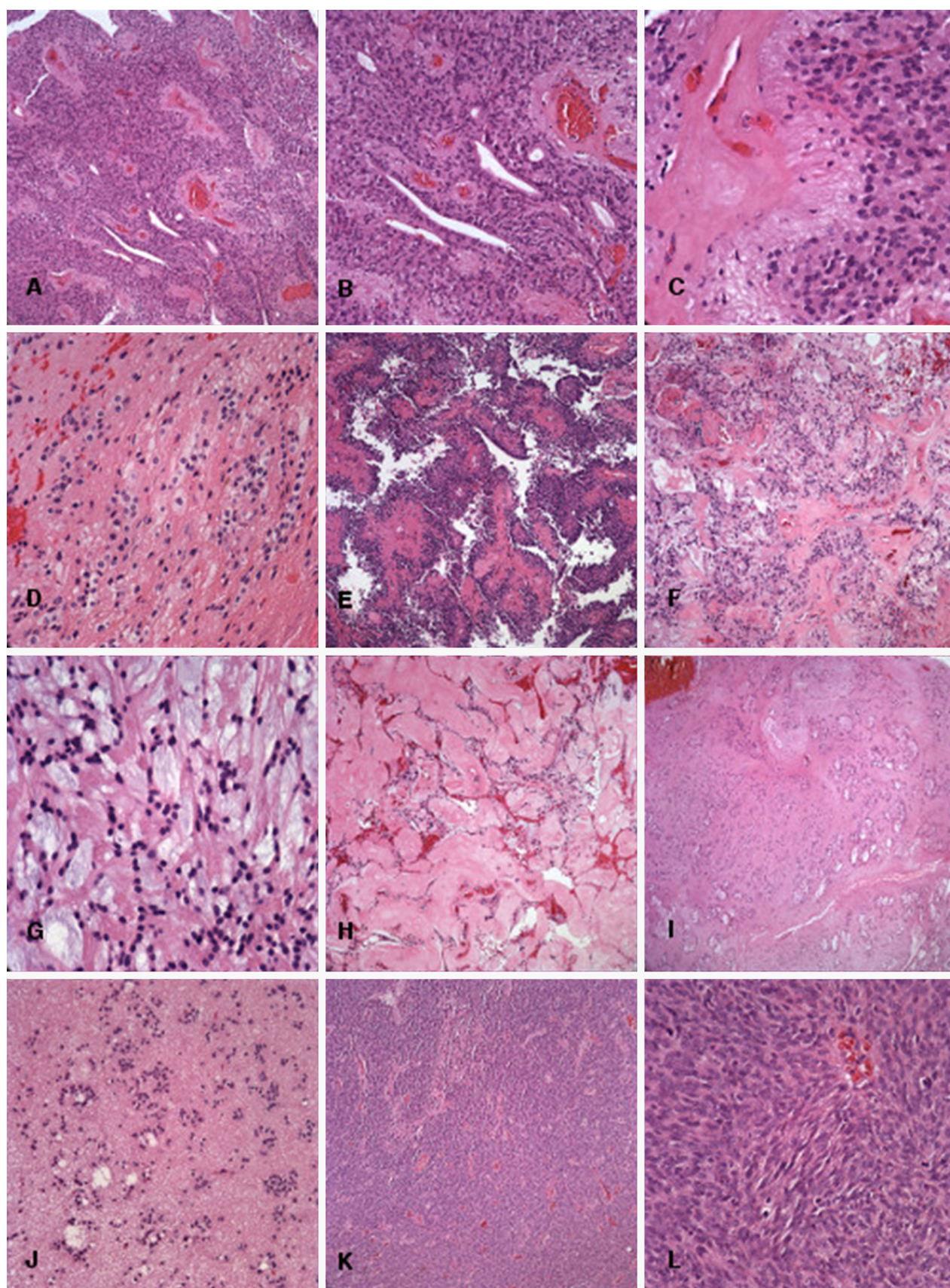


Fig. 1 *a* Grade II ependymoma ($\times 10$) demonstrating high cellularity, perivascular rosettes (pseudorosettes), and true rosettes, *b* grade II ependymoma ($\times 20$) emphasizing true rosettes (*center*) and a large perivascular rosette (*top right*), *c* grade II ependymoma ($\times 40$) emphasizing orientation of cellular processes around perivascular rosettes, *d* Grade II Ependymoma with clear cells, *e* grade II ependymoma, papillary variant, *f* grade I myxopapillary ependymoma ($\times 20$) demonstrating myxoid spaces and hyalinized vessels, *g* grade I myxopapillary ependymoma ($\times 40$) emphasizing myxoid substance between cells, *h* grade I myxopapillary ependymoma ($\times 20$) with high degree of hyalinization, low cellularity, *i* grade I subependymoma ($\times 4$) with microcystic spaces and clusters of cells, *j* grade I subependymoma ($\times 20$) emphasizing clustering of cells on a fibrillary background, *k* Grade III Anaplastic ependymoma ($\times 10$) demonstrating high cellularity and lack of rosettes, *l* grade III anaplastic ependymoma ($\times 40$) emphasizing cellular atypia, nuclear pleomorphism, and mitoses (*arrows*)

(Fig. 1a) [7, 11]. Pseudorosettes, found in several glial tumors, appear as perivascular cuffs of cells with processes oriented towards the central vessel (Fig. 1b, c) [11]. True rosettes, which are more specific to ependymomas, consist of cells arranged similarly around a central lumen (Fig. 1b). The margins of the tumor are typically well-defined on gross and microscopic examination, with compression rather than invasion of the adjacent tissue [6].

Several subtypes of grade II ependymoma are recognized by the World Health Organization (WHO) [5, 11]. Cellular ependymoma is identified by hypercellularity and a high nuclear-to-cytoplasm ratio with few rosettes, but lacks the microvascular proliferation, cellular pleomorphism, or mitoses that correspond to grade III lesions. Clear cell ependymoma is a rare subtype that, like oligodendroglioma, contains perinuclear halos, along with pseudorosettes and sharp histologic borders that differentiate them as ependymoma (Fig. 1d) [6]. Papillary ependymoma is identified histologically by the arrangement of neoplastic cells around a fibrovascular core (Fig. 1e). Tanycytic ependymoma, the least common grade II subtype, is found in the spinal cord more often than the brain and contains cells with long processes similar to pilocytic astrocytes.

Recent studies have demonstrated that location [10, 12] and genetic markers [13] may be more accurate predictors of prognosis than histologic grade. Though the prognostic importance of histologic features is controversial, most large studies show better PFS and overall survival (OS) for grade I or grade II histology compared to grade III [14]. For patients with grade II histology, progression-free survival (PFS) is reportedly 80–90 % at 5 and 10 years [15–17].

Grade III lesions are the least common subtype in adult SCE, characterized histologically by frequent mitoses, endothelial proliferation, and nuclear pleomorphism (Fig. 1k, l) [6]. Unlike grade II ependymomas, anaplastic ependymomas tend to infiltrate surrounding tissue and thus less often allow gross total resection (GTR) [18]. On the

other end of the histologic spectrum, grade I tumors include subependymomas and myxopapillary ependymomas (MPE). Subependymomas have rarely been reported in the spinal cord [19], and may be distinguished by their tendency towards peripheral location within the cord, since other subtypes are typically central. Histologically, subependymomas demonstrate microcystic spaces and grouped cells on a dense fibrillary background (Fig. 1i, j) [11, 19]. Myxopapillary ependymoma is so named for the microscopic appearance of loosely structured cells with intervening pools of mucin, often with markedly hyalinized blood vessels [11] (Fig. 1f–h). In adults, myxopapillary lesions make up approximately one quarter of SCE cases [15, 20]. These tumors occur almost exclusively around the conus medullaris, often involving the cauda equina or filum terminale [6, 21]. Though they lack malignant histological features, MPEs have a higher rate of recurrence than grade II ependymomas [14]. It is unclear how much of this due to the lower rate of GTR in attempts to preserve nerve roots of the cauda equina [11, 14]. Though recurrence may occur in 15–33 % of cases, mortality rates are low, with OS of 85–100 % at 5 years [22].

Imaging

Magnetic resonance imaging (MRI), with and without contrast unless contraindicated, is the best modality to assess suspected spinal cord neoplasms. Perfusion MRI and MR spectroscopy are not typically useful due to the small diameter of the spinal canal and the movement of the spinal cord with arterial blood flow. Computed tomography (CT) provides little diagnostic utility except to identify areas of calcification, and is therefore an alternative only when MRI is unattainable. On PET, ependymomas typically appear hypometabolic due to their low cellular density and slow growth [23].

Cord expansion is a key finding to identify intramedullary tumors; when the cord is normal in size non-neoplastic processes such as a demyelinating disease should also be considered [24]. Relative to the spinal cord, ependymomas are typically hypointense on T1, hyperintense on T2, and enhance with contrast (Fig. 2). They often include areas of cystic change, hemorrhage, necrosis, and/or calcification that may produce a heterogenous signal [24, 25]. Approximately 60 % of ependymomas are associated with an intramedullary cyst rostral or caudal to the tumor [24].

Myxopapillary ependymomas tend to occur in the area of the conus medullaris. Characteristic appearance on imaging is a heterogeneous lesion with isointense cellular components and hyperintense areas of mucin production or hemorrhage (on T1 and T2) [24, 26]. These well-delineated tumors enhance uniformly with contrast.



Fig. 2 MR imaging of a typical cervical spinal cord ependymoma. The majority of the lesion is hyperintense on T2 (*left*) and demonstrates distinct borders and local cord expansion. T1 with contrast (*right*) shows peripheral enhancement with non-enhancing hypo-intense portions that may represent cystic change, necrosis, or hemorrhage

Anaplastic ependymomas are typically T1 isointense, T2 iso- or hyperintense, and have variable contrast enhancement. Infiltration into surrounding tissue may be visible, making them difficult to differentiate from an infiltrative glioma. Due to their high-grade nature, it is important to screen for CNS metastases with MRI of the entire neuraxis and potentially CSF cytology after surgery.

Though there are some radiographic differences between ependymoma subtypes, imaging alone cannot reliably distinguish histologic grade or exclude other diagnoses [24]. Imaging is therefore most useful for pre-operative planning before tissue diagnosis.

Surgical resection

As for most other tumors, the aim of surgery is gross total resection (GTR) with preservation of healthy tissue. Extent of resection for SCE depends on tumor location, size, histology, and the presence of a capsule or syrinx (providing a plane of resection) [12, 17, 27]. The GTR rate for SCE is high (84–93 % of cases), likely because they rarely infiltrate the spinal cord [9].

Multiple retrospective studies have demonstrated an association between extent of resection and progression-

free survival (PFS) in patients with spinal cord ependymoma [14, 27–30]. However, evidence of definitive relationships with PFS or overall survival (OS) are lacking due to the rarity of SCE. Indeed, not all patients may benefit from more complete resection. Oh et al. [12] evaluated the association between clinical outcomes and histologic grading for 175 adult SCE patients across 43 studies. For the cohort as a whole, GTR was associated with better PFS and OS even after controlling for adjuvant radiation therapy. For patients with grade II ependymomas, those with GTR had a significantly lower recurrence rate compared to patients with subtotal resection (STR). In contrast, for grade I myxopapillary ependymoma, the recurrence rate was not significantly different for patients with GTR compared to STR (4/33 patients (12.1 %) versus 6/23 patients (26.1 %) respectively, $p = 0.705$). For grade III ependymoma, the recurrence rate was lower for patients who achieved GTR compared to STR (0/3 patients vs. 6/8 patients), with 5 deaths in the STR group; however, the patient numbers were too small to show a significant difference. Oh et al. also found a significant association between tumor histology and extent of resection, with a higher rate of GTR in SCE patients with grade II lesions (78.8 %) compared to grade I myxopapillary ependymoma (58.9 %, $p < 0.001$), which was greater than the rate of GTR for grade III ependymoma (27.3 %, $p < 0.001$).

Despite efforts to preserve normal tissue, post-operative neurologic deficits are unfortunately common, with risk best predicted by the patient's baseline neurologic function [17, 27]. Compared to patients with deficits at baseline, patients with good neurologic function before surgery are less likely to develop post-operative neurologic symptoms and more likely to improve when symptoms do appear [17]. Patients with thoracic level tumors tend to have more functional deficits after resection, possibly related to the region's relatively limited blood supply and narrow spinal canal [29]. Tumors with more distinct capsules are associated with fewer post-operative neurologic deficits, likely because they are more easily separated from normal tissue [17, 31, 32]. Interestingly, extent of resection has not been found to correlate with post-operative neurologic function [27]. Myxopapillary tumors, due to their typical location near the conus medullaris, have the highest rate of post-operative bladder and bowel symptoms [17, 33]. In cases of MPE, it is important to consider whether maximal resection is worth the potential risk of injury, since evidence of a benefit with GTR is currently lacking for these tumors. Some researchers have suggested that preservation of capsular integrity may be important for preventing recurrence of MPE, however, definitive evidence is currently lacking [34, 35]. Further research is required to define the optimal surgical techniques for preservation of neurologic function and prevention of later recurrence.

Some surgeons have attempted to decrease post-operative morbidity by introducing neurophysiologic monitoring during surgery. Monitoring motor-evoked potentials can detect injury to motor pathways and theoretically prevent further intra-operative damage [29]. Somatosensory-evoked potential monitoring has not been shown to predict functional outcomes [8, 17]. It is difficult to establish whether intra-operative monitoring benefits patients after resection due to the lack of large randomized trials and differences in usage between institutions, but these tools certainly warrant further investigation.

Adjunctive treatments

If full resection is not possible due to tumor location or anatomy, adjunctive radiotherapy (RT) is recommended; however, some studies suggest that adjuvant RT can reduce the rate of progression regardless of the extent of resection [36]. Radiotherapy for SCE typically includes fractionated external beam therapy to a cumulative dose of 54 Gy, which has been shown to improve local tumor control [37]. Craniospinal irradiation (CSI) can be considered for patients with disseminated or metastatic disease. However, studies of CSI are few in number and report mixed results, and not all of these focus on SCE [38]. In 2012, Amsbaugh et al. [39] reported 100 % PFS and OS at 26-months after treating adult SCE patients with proton beam therapy. Because of the lower doses of radiation exposure associated with proton beam therapy, this technique is also an attractive option for pediatric patients.

For patients with surgically untreatable lesions or comorbidities that contraindicate surgery, stereotactic RT may reduce tumor burden, radiation exposure, and treatment-related complications [40]. While the use of RT remains controversial, modern planning techniques have increased precision of targeting, decreasing the effects on surrounding tissue; therefore, with further study radiation may gain support as adjuvant therapy for SCE, specifically for prevention of local recurrence [37].

The role of chemotherapy for treatment of SCE is even less clear than that of radiation. Although few in number, some studies suggest chemotherapy as salvage therapy for recurrence if both surgery and RT fail. Only one prospective study of chemotherapy for SCE has been published: Chamberlain reported outcomes of ten adult patients with recurrent, low-grade, intramedullary SCE treated with oral etoposide [41, 42]. All ten patients had experienced recurrence after surgery and RT, and 4 had failed prior attempts with chemotherapy. Outcomes were progression in 3 patients, partial response in 2 patients, and stable disease in 5 patients. Median PFS was 15 months (range 2.5–45 months), and median OS was 17.5 months (range

3–45 months). The drug was well tolerated, but without a phase II trial, the efficacy of etoposide compared to other regimens is unknown.

Molecular genetics

On molecular analysis, SCE frequently demonstrates loss of chromosome 22q, although no specific tumor suppressor genes in this region are consistently altered [43]. Although *merlin* (NF2) is located on chromosome 22q, there is no evidence for its involvement in the pathogenesis of SCE [43, 44]. Myxopapillary ependymomas have the most genetic abnormalities of all SCE subtypes, specifically mutations in chromosome 7 [45].

Immunolabeling techniques have been used to investigate mutations implicated in SCE tumorigenesis and to explore prognostic markers. Although p53 alterations are rare in SCE, the MDM2 gene, which regulates p53-mediated cell growth, has been found to be amplified and overexpressed [46]. Furthermore, p53 expression may be higher in grade II and III ependymomas than in subependymomas, although this difference is not statistically significant [47]. However, Ki-67, a nuclear protein associated with proliferation, was found to increase in expression from grade I to grade III SCE and thus could serve as a prognostic marker.

The ErbB protein family has also been investigated as a therapeutic target in SCE [48]. ErbB 2 (Her2) and ErbB 4 co-expression has been demonstrated in over 75 % of ependymomas, and ligand-dependent activation of the ErbB receptor triggers cellular proliferation in cultured ependymoma cells. This proliferation signaling cascade was subsequently blocked in a dose-dependent manner by a novel inhibitor of ErbB 2 tyrosine kinase [49]. In addition, Kong et al. [50] in 2014 demonstrated suppression of ependymal cell growth after treatment with topoisomerase inhibitor (WP744) as well as p-STAT3/HIF- α inhibitors (WP1066 and WP1193), possibly suggesting further molecular therapeutic targets in SCE.

Our cohort of patients

The current study reports ten adult patients with histologically confirmed SCE who underwent resection at Emory University Hospital Midtown from 2007 to 2013. The median length of follow-up after surgery was 40.3 months (range 24–79 months). Patients had a mean age of 41.5 years and included seven males, three females. Symptoms preceded diagnosis by an average of 22.8 months (range 3–48 months). Symptoms worsened acutely in 3 patients before surgery, with one confirmed

Table 1 Data of our ten-patient cohort

Vertebral level	Age/sex	Gender	Presenting symptoms	Symptom duration (months)	Intra- versus extramedullary	Syrinx	Histology	Surgery	Surgical complications	Radiation	Recurrence (months)	Follow-up (months)
Medulla	25	F	Back/neck pain Lower extremity radicular pains	3	Intramedullary	N	Ependymoma, grade unspecified	Biopsy	N	FRS brain + complete spine	17.4	94.1
C3-4			Lower extremity stiffness/hyperreflexia		Intramedullary	Y	Grade II	Initial surgery: biopsy, Repeat surgery: gross total	N		N	
T4-6			Upper and Lower extremity paresthesias		Intramedullary	Y	Grade II tanyctic	Gross total	N		N	
T10			Balance difficulty		Intramedullary	N	/	None	N		N	
T11-12			Syncope Nausea/Vomiting Headaches		Intramedullary	N	/	None	N		N	
C4-5	40	M	Diplopia Upper extremity weakness	6	Intramedullary	N	Grade II classic	Gross total	N	FRS local	N	24.0
C5-T1	42	M	Upper extremity paresthesias Unilateral sensory loss Back/neck pain Upper extremity weakness, unilateral	9	Intramedullary	N	Grade II classic	Gross total	N	FRS local	N	63.9
C4-C7 (cyst medulla-T7)	42	M	Upper extremity sensory loss Upper extremity radicular pains & paresthesias Back/neck pain Upper extremity weakness, unilateral	24	Intramedullary	Y	Grade II classic	Sub-total	CSF leak	FRS local	N	29.4
T1-T2	49	F	Upper extremity sensory loss, unilateral Upper extremity paresthesias, unilateral Balance difficulty	6	Intramedullary	N	Grade II classic	Gross total	N	FRS local	N	41.6

Table 1 continued

Vertebral level	Age/sex	Gender	Presenting symptoms	Symptom duration (months)	Intra- versus extramedullary	Syrinx	Histology	Surgery	Surgical complications	Radiation	Recurrence (months)	Follow-up (months)
T1–2 (cyst C6–T4)	47	M	Lower extremity sensory loss Lower extremity stiffness/hyperreflexia	36	Intramedullary	Y	Grade II tanycytic	Gross total	N	N	N*	0.1*
T4	50	M	Back pain Lower extremity weakness Bladder/Bowel incontinence	36	Intramedullary	N	Grade II classic	Gross total	N	N	N	39.4
T8 (cyst T7–T9)	62	M	Balance difficulty Lower extremity sensory loss Lower extremity paresthesias Bladder incontinence	24	Intramedullary	Y	Grade II classic	Gross total	N	FRS local	N	40.8
T12–L5	21	F	Balance difficulty Back pain Lower extremity radicular pains	48	Extramedullary	N	Grade I myxopapillary	Sub-total	N	FRS local**	N	29.4
L2–3	37	M	Back pain	36	Extramedullary	N	Grade I myxopapillary	Gross total	N	N	N	40.3
Median	42		Median	24							Median	40.3
SD	12		SD	16							SD	22
Min	21		Min	3							Min	24.0
Max	62		Max	48							Max	94.1

* This patient expired a few weeks after surgery while admitted to an acute rehab facility

** This patient received proton-beam therapy

case of intra-tumoral hemorrhage. Individual patient data appears in Table 1.

All ten patients were treated surgically. Figure 3 shows pre- and post-operative images for GTR of a tumor in the cervical region. Seven patients were treated with adjunctive fractionated radiation therapy, none with chemotherapy. Only one patient had demonstrated tumor recurrence, defined as radiologic or clinical evidence of disease

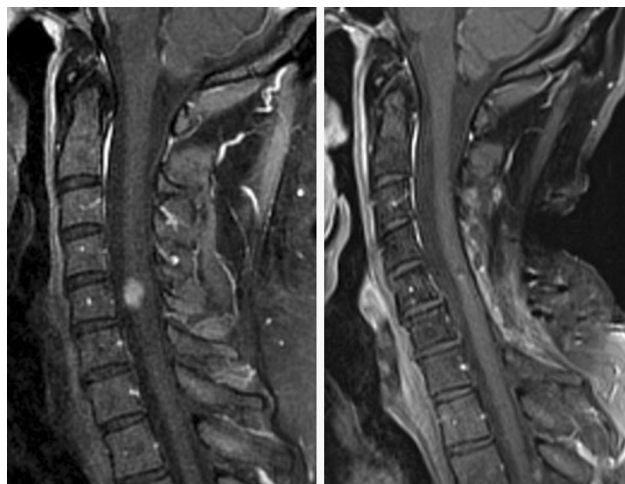


Fig. 3 Sagittal cervical T1 post-contrast MR images of our second patient (40-year-old male, C4-5 lesion) from Table 1. Preoperative image (*left*) shows characteristic cord expansion and hyperintense tumor with evidence of hemorrhage, necrosis, or calcification. Postoperative image at 2 year followup (*right*) confirms gross total resection

progression over the follow-up period. Follow-up was measured from initial surgery to the last documented neurologic evaluation. One patient expired several weeks after surgery at an outside acute rehab facility; he was reported to have died from a pulmonary embolism. This patient was not included in follow-up calculations. There was one post-operative complication, a cerebrospinal fluid leak; no post-operative infections or hematomas were reported.

Functional outcomes are shown in Table 2. Post-operatively, there were 14 instances of new or worsened neurologic symptoms (transient in 4 cases), 8 instances of immediate improvement of a pre-operative symptom, and 9 instances of delayed symptom improvement. Overall, new deficits occurred after 8 out of 13 surgeries, and immediate or delayed improvement of at least one symptom occurred after 9 out of 13 surgeries. Common post-operative deficits included focal weakness or sensory loss, some developed delayed paresthesias or radiculopathy. Over time, the majority of patients improved, with one patient developing progressive symptoms of radicular pain, weakness, and sensory loss after radiation.

An operative microscope was used for all surgeries; neurophysiologic monitoring with somatosensory evoked potentials (SSEP), electromyography (EMG), and motor evoked potentials (MEPs) was used in all except two surgeries. Two cases had abnormal MEP signals: one with a loss of lower extremity MEPs partway through surgery for a lesion at T2, the other with poor baseline lower extremity MEPs (surgery for a T12-L5 lesion). The

Table 2 Symptom changes after surgery

Unique patient #	Tumor location	Pain	Weakness	Sensory loss	Paresthesias	Incontinence
1	C3–4 (biopsy)	+	–	–	++	0
1	T4–6	0	++	=	0	–
1	C3–4	–	–	=	0	0
1	Medulla (biopsy)	0	=	=	0	0
2	C4–5	0	++	+	+	0
3	C5–T1	++	+	–	+	0
4	C4–7 (cyst medulla-T7)	++	–	–	–	0
5	T1–T2	=	+	–	=	0
6	T1–2 (cyst C6–T4)	0	–	=	0	+
7*	T4	=	–	–	0	+
8	T8 (cyst T7–T9)	0	–	=	++	=
9*	T12–L5	+	0	0	++	0
10	L2–3	++	0	0	0	0

Each row represents one surgery, comparing pre- and post-operative symptoms. All patients had one surgery, except for the first who underwent multiple surgeries for recurrences

* These patients had abnormal results on neurophysiologic monitoring before or during surgery, see text

++ immediate improvement, + delayed improvement, 0 symptom was never present, = no change, – transient new deficit, – new or worse deficit

functional outcomes for these patients are indicated in Table 2. The first of these patients was a 50-year-old male with a long history of degenerative disease of the spine with several previous surgeries whose tumor at the level of T4 was first discovered incidentally, unaccompanied by neurologic symptoms. He refused recommended surgery for resection until 2 years after the tumor was seen on MRI, when he developed acute thoracic pain, lower extremity weakness, and incontinence of bladder and bowel and had urgent surgery. After surgery, he had worsening bilateral lower extremity weakness that has persisted over follow-up for more than 5 years, though his incontinence and thoracic spine pain resolved. The second patient was a 21-year-old female with back pain radiating into the legs on presentation, after surgery her pain resolved and she had no new neurologic symptoms immediately post-operative or during 3 years of follow-up. SSEPs, MEPs, and EMG remained stable throughout all other surgeries. In this small cohort of patients, there were no significant relationships between tumor features, neurophysiologic data, and functional outcomes.

Discussion

Due to the rarity of SCE, there is a paucity of data available to enable creation of consensus regarding optimal management of these patients. This paper represents an effort to fill this void with a systematic review of published literature describing multiple aspects of SCE, ranging from its pathophysiology to imaging characteristics and treatment recommendations. In addition, a case series of 10 patients managed surgically at Emory University Hospital Midtown has been included in an effort to contribute to published knowledge regarding the presentation and prognosis of this rare spinal cord tumor.

Findings of our patient cohort data match those of previously published cases. Mean age at diagnosis was 41.5 years in our cohort, similar to averages reported in the literature [9, 17]. In addition, the most common symptom at diagnosis in our cohort was back pain, followed by sensory loss and weakness, similar to previously published reports [7, 20]. Both myxopapillary tumors found in this cohort were extramedullary and located around the filum terminale, in keeping with previous reports of the typical location of this tumor subtype [8, 21, 34]. The case of the one patient with multiple grade II tanycytic tumors demonstrates the potential for aggressive behavior possessed by ependymomas, even in a histologic subtype reported to have a good prognosis [51].

Generalizability of the reported cohort is limited by the small number of patients and brief periods of follow-up given relatively recent dates of surgery. Nonetheless, the

management of these patients reflects the use of current management strategies in the treatment of SCE, including surgical resection with neurophysiologic monitoring and potential adjuvant radiotherapy. This data aims to contribute to larger scale analyses of patient outcomes required to determine optimal management strategies for future patients with this rare tumor.

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