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Primary intradural Ewing's sarcoma of the spine: a systematic review of the literature

Victor M. Lu[a,b,1], Anshit Goyal[b,c,1], Mohammed Ali Alvi[b,c], Panagiotis Kerezoudis[b,c], Michael G. Haddock[d], Mohamad Bydon[b,c,*]

[a] Prince of Wales Clinical School, Faculty of Medicine, University of New South Wales, Sydney, Australia
[b] Mayo Clinic Neuro-Informatics Laboratory, Mayo Clinic, Rochester, MN, USA
[c] Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA
[d] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

The incidence of extraosseous Ewing's sarcoma, a highly malignant mesenchymal mass, is rare in the spinal cord and its clinical outcomes unknown. To date, few cases of primary intradural extramedullary Ewing's sarcoma (PIEES) have been reported, with varying follow-up. Herein, we aimed to perform a comprehensive review of all cases published in the literature and update previously reported cases from our institution. Institutional medical records were searched for cases of PIEES of the spine managed at our institution between the years 2005 and 2018. We performed a systematic search of two electronic databases (Ovid Medline and Embase) from inception to August 2018 to obtain all published cases of primary intradural extraosseous Ewing's sarcoma (PIEES).We used our institutional medical records to update cases reported from our institution. We identified a total of 44 cases with pIEES reported in the existing literature of which 5 have been from our department. Of the 41 cases, the median age of diagnosis was 31 years. The most common presentation pattern was PIEES in the lumbar/sacral region (61%, n = 27), with a majority (59%, n = 25) presenting initially with pain. The most common modality of treatment reported was surgery (41/41, 100%), followed by adjuvant chemotherapy (31/44, 70%) and local radiation therapy (29/44, 66%). Overall, recurrence was reported in 17/36 (46%) cases, with median progression free survival (PFS) of 12 months (range, 1–72). There were 12/37 (32.4%) deaths reported, with median overall survival (OS) of 14 months (range, 1–72). Hence, we present the most updated review of all reported cases of PIEES. While surgical resection is the mainstay of treatment, tumor recurrence is a great concern given the adhesive nature of the lesion preventing complete resection. Adjuvant chemotherapy and radiotherapy should be carefully considered to prevent recurrence and improve survival outcome.

1. Introduction

Ewing's sarcoma (ES) is a mesenchymal tumor characterized by small, round, blue cells, and is poorly differentiated and highly malignant [1]. While ES typically arises in bone and soft tissue, rare primary extraosseous manifestations of ES have been reported throughout the body [2]. Specifically, the incidence of primary intradural, extramedullary ES (PIEES) of the spine is extremely rare. To date, there have been only a few cases reported in the literature

PIEES shares many histological features with its osseous counterpart. However, extraosseous ES has been associated with superior overall survival (5-year survival: 70% vs 62%) compared to its osseous counterpart [3]. Moreover, the adhesive nature of PIEES in relation to the spinal cord and nerve roots may prove to be a barrier in achieving complete resection without neurological compromise. Also, given the established recurrent and metastatic nature of ES, the presence of PIEES within the central nervous system renders patients vulnerable to further tumor in more precious and delicate areas relative to other extraosseous sites [4].

We previously reported 5 cases with PIEES from our institution who received surgical resection [5,6]. In this study, we present an update on three of those cases and review the other two. We also conducted a systematic review of the literature for PIEES of the spine and summarized the clinical outcomes of all published cases. Although

* Corresponding author: Department of Neurosurgery, Mayo Clinic, 200 First Street SW, Rochester, MN, USA.
E-mail address: bydon.mohamad@mayo.edu (M. Bydon).
[1] These authors contributed equally to this work.

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extremely rare, the possibility of PIEES in a patient that presents with an intradural mass should not be prematurely dismissed.

2. Materials and methods

Following Institutional Review Board (IRB) approval, we queried our institutional medical records from 1992 to August 2018 for histopathologically confirmed cases of primary intradural extraosseous Ewing's sarcoma or peripheral primitive neuroectodermal tumor in any age group. Cases with osseous, metastatic, extradural or intramedullary disease at time of diagnosis were excluded. We also systematically searched PubMed and Medline databases from inception to August 2018 using a combination of the following keywords: intradural, Ewing sarcoma or peripheral primitive neuroectodermal tumor, extramedullary, spinal cord, spine. Two reviewers (V.M.L., A.G.) independently reviewed all cases to assess eligibility for inclusion. We also identified cases from our institution that had been previously reported in the literature and obtained latest follow up data from the medical records.

3. Results

We identified a total of 44 cases published in the literature, of which 5 had been reported from our institution. No new unreported cases were identified from our search of institutional medical records.

3.1. Case 1

3.1.1. Presentation and investigation

We previously reported a 50-year-old male who presented with loss of ambulation secondary to rapidly progressive lower extremity weakness, saddle anesthesia, and loss of bowel and bladder control. The patient had 1 month of bilateral lower limb numbness, and 3 months of shooting pains in the hip and buttock regions. Upon examination, the patient was found to have diffuse weakness, and loss of sensation, in both lower limbs. Reflexes were reduced at the knees, and absent at the ankles, with plantar responses equivocal. Magnetic resonance imaging (MRI) revealed an intradural extramedullary mass extending from the upper aspect of T11 to upper aspect of L1 **[**Fig. 1**(A)]**. There was notable mass-effect with marked central stenosis and cord compression at the T12-L1 level. Multiple areas of cystic change were seen within the mass, which was otherwise homogeneous in enhancement.

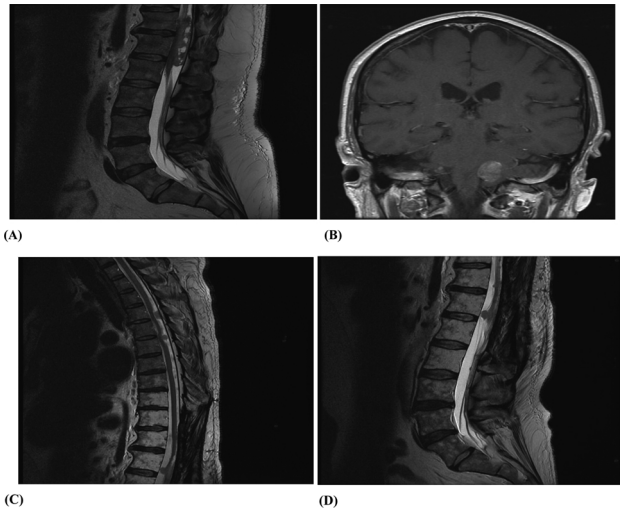

Fig. 1. T2 weighted MR images showing (A) Primary intradural tumor extending from T11-L1 with cord compression and stenosis (B) Metastasis to the cerebellopontine angle (C) Recurrent intradural thoracic spine metastases (D) Recurrent intradural lumbar spine metastases.

3.1.2. Operative findings

In the light of the acute deterioration, the patient underwent a T10 to L1 laminectomy. Upon elevation of the dura, an encapsulated fleshy mass with areas of intralesional hemorrhage at both poles was found. Mobilization was difficult due to dense adhesions so the contents of the lesion were internally debulked. The majority of the capsule was removed piecemeal except for a small part which had invested the ventral nerve rootlets. There were no intraoperative complications and immediate postoperative course was unremarkable. Histopathological examination was positive for CD 99 (MIC 2), CD 56, pancytokeratin (AE1/AE3), OSCAR, CAM5.2 and synaptophysin. Molecular analysis showed positive EWSR1-FLI1 fusion transcript by RT-PCR.

3.1.3. Postoperative course

The hospitalization of the patient was uneventful and he was discharged to rehab being able to ambulate with assistance. He was subsequently managed with six cycles of chemotherapy consisting of vincristine, cyclophosphomide, and Adriamycin on odd cycles alternating with ifosfamide and etoposide on even cycles followed by local radiation therapy, 5040 cGy in 28 fractions. He tolerated this regime well, and his physical and neurological functions were deemed satisfactory at cessation.

The patient subsequently had metastasis to the brain **[**Fig. 1**(B)]** near the cerebello-pontine angle followed by multiple metastases to the spine **[**Figs. 1**(C), (D)]**. Despite surgical removal of the brain metastasis, chemotherapy and craniospinal radiation, the patient expired 5 years after the initial diagnosis.

3.2. Case 2

3.2.1. History and Presentation

We previously reported a 25-year-old male who presented to an outside institution with two week history of weakness in both upper limbs, and pain in the posterior neck. Upon examination, strength was decreased in both upper limbs. MRI revealed a contrast enhancing intradural extramedullary mass between C3 and C7. The patient underwent a C2 to T1 laminoplasty and durotomy. The tumor was noted to be adherent to the ventral spinal cord, and subtotal resection was performed to preserve cord integrity at the outside hospital.

Three weeks after the initial surgery, the patient presented at our institution with loss of ambulation, numbness in upper limbs and incomplete control of bowel and bladder. Upon examination, there was distinct weakness in all limbs. Furthermore, in all limbs, sensation was decreased to both pin prick and light touch, and reflexes were brisk. Clonus was elicited in both ankles. MRI now showed a partially resected intradural mass from C4 to C7 with probable residual extension out the right C5 to C6 neural foramen. There was increased compression of the spinal cord and increased spinal cord T2 hyperintensity.

3.2.2. Operative findings

Re-exploration of the laminoplasty revealed a bulging and edematous spinal cord with no evidence of a CSF leak or hematoma. A highly vascular extramedullary tumor was encountered which was dorsally displacing the cervical nerve roots. A second, but more extensive subtotal resection was performed followed by a generous duraplasty and C3-T1 fusion. Histopathological examination showed a small blue cell tumor positive for CD99, negative for actin, desmin, MYOD1, chromogranin, synaptophysin, WT-1 and CAM 5.2. EWSR1-FLI1 fusion transcript was positive by FISH (Fluorescence in situ Hybridization) analysis.

3.2.3. Postoperative course

The patient experienced a prolonged recovery course in hospital. His course was complicated by progressive neck pain and urinary retention, with MRI showing development of a cervical syrinx. Urgent 200cGy radiation and steroids were administered. During the

hospitalization, the patient received his first cycle of chemotherapy ifosfamide and etoposide. This was complicated by an episode of pancytopenia. He was discharged home five weeks after his initial presentation to our institution. He was managed by craniospinal radiation therapy, 5400 cGy to the spine and 3600 Gy to the brain in 20 fractions, then by multiple chemotherapy cycles which added vincristine, doxorubicin and cytoxan in various combinations. This was ultimately ceased prematurely due to the recurrent myelosuppression, severe mucositis, esophageal strictures and cardiac complications with decreased ejection fraction. Surveillance was then commenced. At last follow-up 62 months after initial diagnosis, there was no evidence of recurrence.

3.3. Case 3

3.3.1. Presentation and investigation

We previously reported a 60-year-old male who presented with two month history of low back pain radiating to bilateral lower extremities. Upon examination, patient was found to have radiculopathy in bilateral L3 dermatomal distribution. MRI revealed a contrast enhancing intradural extramedullary mass at L2 to L3.

3.3.2. Operative findings

The patient underwent a L2 to L3 laminectomy to reveal the tumor for resection. Upon entry into the dural space, a red, friable, vascular mass was found. There was no attachment to the dura, and upon invasion of the arachnoid, a lumbar nerve root was seen to be entering and exiting from the mass. It was decided to proceed with subtotal resection in order preserve the nerve root. There were no intraoperative complications and immediate postoperative course was unremarkable. Immunohistochemistry showed strong positivity for CD99(MIC2) with focal immunereactivity for CAM5.2, synaptophysin and vimentin.RT-PCR analysis confirmed presence of the EWSR1-FLI1fusion transcript.

3.3.3. Postoperative course

The patient had an uneventful recovery course in hospital with some neurological improvement. He was discharged five days after surgery, and subsequently managed with two cycles of ifosfamide and etoposide alternating with two cycles of ifosfamide and Adriamycin prior to radiation therapy, then a break for radiation therapy of 5040 cGy in 28 fractions to the spine, and then resumption of chemotherapy with two more cycles of ifosfamide/etoposide alternating with ifosfamide/Adriamycin. He tolerated this regime, with no significant comorbid events.

Eleven months after initial diagnosis, the patient was subsequently found to have asymptomatic intradural metastasis to the cauda equina followed by diffuse leptomeningeal spread to the cervical and thoracic spine. Lesions were also detected at the foraminae of Magendie and Luschka. His metastatic burden continued to progress despite administration of chemotherapy and craniospinal radiation and succumbed to his disease 4 years after the initial diagnosis.

3.4. Case 4

3.4.1. Presentation and investigation

We previously reported a 34-year old male who presented with cauda equina syndrome at an outside facility. MRI demonstrated an intradural tumor at L4-5 with three nodular lesions at S1-S2 and S4-S5 nerve roots.

3.4.2. Operative findings

He underwent complete surgical resection of the tumor at L4-5, however, he was left with residual disease at the sacral level. Pathologic examination showed a small blue cell tumor positive for CD99, synaptophysin and EMA. Molecular analysis was positive for EWSR1-FL11 fusion transcript.

3.4.3. Postoperative course

Following surgery, he received 5 alternating cycles of chemotherapy with vincristine, doxorubicin, cyclophosphamide and ifosfamide, etoposide along with growth factor and autologous stem cell support. Following 3 cycles of chemotherapy, he demonstrated a complete response on imaging at both L4-L5 level and other disease sites. After a discussion of risks and benefits, he decided to proceed with spinal radiation but not cranial radiation. He received entire spine radiation at a dose of 3000 cGy with a boost to 5940 cGy. Following completion of therapy, he remains disease free after 24 months of follow-up.

3.5. Case 5

3.5.1. Presentation and investigation

We previously reported a 61-year-old male who presented with a two week history of episodic, severe alternating pain in bilateral lower limbs in the L3-L4 distribution. He also noted perineal numbness and occasional difficulty with urination during this period. Physical examination revealed weakness on left knee flexion. Knee and ankle jerk reflexes were absent with equivocal plantar responses. MRI revealed an intradural extramedullary mass extending from L1 to L3.

3.5.2. Operative findings

The patient underwent a T12 to L3 laminectomy to reveal the tumor for resection. Upon elevation of the dura, a large unencapsulated hemorrhagic mass in the subarachnoid space compressing the cauda equina was observed. After arachnoid dissection, the tumor was removed piecemeal by suction, without significant difficulty. Parts of the tumor were adherent to the lumbar nerve roots, and were removed under electromyography (EMG) monitoring. Microscopic inspection ensured gross total resection without any intraoperative complications. Histopathology and molecular analysis confirmed the diagnosis of Ewing's sarcoma.

3.5.3. Postoperative course

The patient had an uneventful recovery course in hospital. He was discharged to home five days after surgery, being able to ambulate with assistance. He was subsequently managed with five cycles of chemotherapy consisting of combinations of vincristine, cyclophosphomide, Adriamycin, Ifosfamide, Etoposide and cisplatin followed by radiation therapy of 5040 cGy in 28 fractions to the spine. At last follow-up 12 months after initial diagnosis, there was no evidence of recurrence.

3.6. Review of the literature

The cases reported in this study illustrate the heterogeneous clinical course of PIEES. They are collectively and individually described in Tables 1 and 2 respectively. In the 44 cases, the median age of diagnosis is 31 years, with 70% (n = 31) male incidence. The most common location was the lumbar/sacral region (61% n = 27), with 59% (n = 26) of patients presenting with a chief complaint of pain, and 41% (n = 18) with a chief complaint of weakness. The average duration of the chief symptom was 3 months. Preoperative or intraoperative evidence of intratumoral bleeding was found in nine (20.4%) cases. The most common modality of treatment reported was surgery (100%, 44/44) followed by adjuvant chemotherapy (70%, n = 31) and local radiation therapy (66%, n = 29). Gross total resection was achieved in 65% (28/44) of cases, and median radiation dose was 5000 to the spine. Overall, recurrence was reported in 46% (17/36) of cases, with a median progression free survival (PFS) of 12 months (range: 1–72). PFS is shown in Fig. 2**A**. There were 10/34 (29.4%) deaths reported, with median overall survival (OS) of 14 months (range:1–72). Overall survival in shown in Fig. 2**B**.

Table 1
Summary of all reported cases and outcomes of PIEES of the spine published in the literature to August 2018. STR, subtotal resection; GTR, gross total resection; PFS, progression free survival; OS, overall survival.

Characteristic	Value
Cohort size (n)	44
Median age, range (yrs)	31, 5-70
Gender (n,%)	
Male	31, 70%
Female	13, 30%
Location (n, %)	
Cervical	9, 20%
Thoracic/Thoracolumbar	8, 18%
Lumbar/sacral	27, 61%
Chief symptom (n, %)	
Pain	26, 59%
Weakness	18, 41%
Median duration of symptoms, range (mos, n = 24)	3, 0.3-12
Initial treatment	
Surgery	44/44, 100%
STR	15/44, 35%
GTR	28/44, 65%
Chemotherapy	31/44, 70%
Radiation	29/44, 66%%
Median dose, IQR (cGy, n = 19)	5000, 4000-5042
Outcomes	
Median PFS, range (mos, n = 33)	12, 1-72
Recurrence (n, %)	17/36, 46%%
Median OS, range (mos, n = 34)	14, 1-72
Deaths (n, %)	12/37. 32.4%

4. Discussion

The molecular profile of PIEES is emerging as a critical component in diagnosis. Classically, ES demonstrates oncogenic chromosomal rearrangements involving the *EWSR1* gene along chromosome 22, which has become pathognomonic of the disease [40]. The most common rearrangements are the nonrandom translocations t(11,22)(q24;q12) and t(21,22)(q22;q12), which occur in approximately 85% and 10–15% of all cases respectively [40]. The former is characterized by the EWSR1-FLI1 fusion transcript on molecular analysis. Rarer translocations with chromosomes 2 (*FEV*), 7 (*ETV1*) and 17 (*ETV4*), as well as gains of chromosomes 1q, 2, 5, 7, 8 and 12 and deletions of chromosomes 1p36, 9p, 17p and 16q have all been reported as well [41,42]. Thus the absence of the classic t(11,22)(q24;q12) does not necessarily dismiss the diagnosis of PIEES.

Histological examination has been the traditional means for diagnosis. Microscopic imaging of small, round, blue cells accompanied by positive CD99 antigen expression supports a diagnosis of ES. CD-99 is a 32-kDa cell membrane glycoprotein which may inhibit cellular differentiation in ES via modulation of the MAPK pathway [43]. Unfortunately, CD99 expression is not entirely specific for ES, as it is also expressed in other primitive neuroectodermal tumors. A positive molecular EWSR1-FLI1 fusion transcript is considered an important diagnostic feature for PIEES [44]. While our series involved molecular confirmation by either FISH or RT-PCR, there were several cases in the literature in which the diagnosis was based only on histopathology and immunohistochemistry. The fidelity of the diagnosis could not be completely ascertained in such cases, although they were reported as Ewing's sarcoma. It must also be remembered that peripheral primary neuroectodermal tumors (pPNETs) are virtually indistinguishable from Ewing's sarcoma with a positive EWSR1-FLI1 fusion transcript and strong positivity for CD99. Given their similarity, it has been argued that they are the same pathologic lesion as extraosseous Ewing's sarcoma, falling within the spectrum of "Ewing family of tumors (EFT)". In light of these findings, several cases in the literature reported their findings as "Ewing's sarcoma/pPNET". It must be noted that, for the very same reason, we were unable to perform accurate histologic discrimination between the two types of tumors in our own series. In contrast to osseous Ewing's sarcoma, we found most patients in our series to present in late adulthood (median age-31 years). We also found poor 5-year overall survival in our series (40%, Fig. 2B**),** whereas, in contrast, literature has previously suggested higher 5-year survival in extraosseous Ewing's sarcomas (70%), even when compared to osseous lesions (62%) [3].

The pathogenesis of formation of an intradural tumor is unclear. Initially, several lines of evidence suggested a neural crest cell of origin for Ewings's sarcoma based on expression of neuroectodermal markers on tumor cells [45,46]. However more recently, studies have shown that expression of EWSR1-FL11 fusion transcript upregulates expression of neural crest genes in bone marrow cells, fibroblasts and other cell types [47–49]. This suggests that expression of EWSR1-FL11 might play a larger role in Ewing's sarcoma neural phenotype than cell of origin itself [50].

For surgical management, it has been shown that complete resection with negative margins of extraosseous ES confers a statistically significant survival advantage [51]. While there is no evidence specific to PIEES, it is worth noting anecdotally that of all death events reported in the literature, 60% (6/10) involved subtotal resection. The use of minimally invasive surgery for removal of intradural extramedullary lesions has been reported in the literature [52]. A significant proportion of patients in the literature review presented with acute decompensation due to intratumoral hemorrhage and intraoperatively, a high degree of vascularity was encountered in general, which is also an important consideration for surgical resection. Given the adhesive, infiltrative and vascular nature of the tumor, especially around nerve roots, the use of neuromonitoring such as EMG should be considered to avoid injury to the neural elements.

In terms of adjuvant therapies, the roles of radiation therapy and chemotherapy are still being established. In their meta-analysis of extradural ES, Saeedinia et al. [53]. found a survival advantage at 1-year when both modalities were administered together versus singularly. However, this advantage was lost at the 2-year follow-up. Radiation to the spine remains a challenge for management. The safety threshold for radiation to the spinal cord is 50–55 Gy to minimize the risks of myelopathy, deformity, fracture, fibrosis and secondary malignancies [54]. However, this safety threshold is below the optimal dose 56–60 Gy recommended to treat osseous ES without surgical resection, and thus it might pose a sub-therapeutic risk in PIEES with gross residual disease [55]. Apart from gross residual disease, the possibility of microscopic seeding from a friable tumor needs to be taken into consideration while considering the optimal course for adjuvant radiotherapy [7]. Advances in understanding the potential benefits of preoperative radiation, and the applicability of stereotactic radiosurgery in lesional targeting are exciting areas of investigation which will help advance the management of these lesions.

Although the optimal chemotherapy regime to treat PIEES is unknown, current recommendations for osseous ES have also been suggested as the initial regime for PIEES. This includes alternating cycles of vincristine, doxorubicin, and cyclophosphamide with ifosfamide and etoposide [56]. A number of clinical trials are underway investigating regimes that may provide greater control for metastatic disease in osseous ES, which may have some role in managing PIEES recurrence later on since these areas are well supplied by spinal arteries [57,58]. However, in cases such as Cases 1 and 3 in our series, where metastases to the brain occur, the potential benefit of the same chemotherapy regime will be reduced due to the need to penetrate the blood brain barrier (BBB). Limited evidence from literature for other extraosseous Ewing's sarcomas also indicates that adjuvant chemotherapy and radiotherapy may improve survival [2]. The small sample size in our review supplemented with the heterogeneity in reporting precluded outcome comparisons between different treatment modalities.

Table 2
Individual outcomes for all reported cases and outcomes of extraosseous PIEES of the spine published in the literature to August 2018. M, male; F, female; C, cervical; T, thoracic; L, lumbar; S, sacral; R, right; L, left; UL, upper limb; LL, lower limb; LBP, lower back pain; GTR, gross total resection; STR, subtotal resection; PFS, progression-free survival; OS, overall survival; Y, yes; N, no; A, alive; D, dead.

Case	Author	Age, Gender	Location	Chief presenting symptom(s)	Duration of any symptoms	Positive EWS-FL11 fusion transcript/Chromosome 22q12 translocation	Intratumoral hemorrhage	Initial treatment			Outcome after initial diagnosis (mo)			
								Surgery	Chemotherapy	Radiation (cGy)	PFS	Recurrence	OS	Status
1	Case 1/Chihak et al 2016 [5]/Mateen et al [6]	50, M	T11-L1	LL weakness	3	Yes	Yes	STR	VCR, CTX, ADR, IFO, VP16	5040	48	Y	60	D
2	Case 2/Chihak et al 2016 [5]	25, M	C3-C7	UL weakness, neck pain	0.5	Yes	No	STR	VCR, CTX, ADR, IFO, VP16	5400	62	N	62	D
3	Case 3/Chihak et al 2016 [5]/Mateem et al 2011 [6]	60, M	L2-L3	LBP, LL pain	2	Yes	No	STR	ADR, IFO, VP16	5040	11	Y	48	D
4	Case 4/Chihak et al 2016 [5]	34, M	L4-L5	LBP, LL pain	–	Yes	No	GTR	VCR, AMD, CTX, IFO, VP16	5940	24	N	24	A
5	Case 5/Takami et al 2018 [7]	61, M	L1-L3	LL pain	0.5	Yes	Yes	GTR	VCR, CTX, ADR, IFO, VP16, CPPD	5040	12	N	12	A
6	Paterakis et a. 2017 [8]	31, M	L2-L3	R-LL weakness	–	Yes	No	GTR	VCR, AMD, CTX, DACT, IFO, VP16	–	24	Y	42	A
7	Bostelmann et al. 2016 [9]	29, M	C7	R hemiparesis	3	Yes	No	GTR	VCR, IFO, AMD, VP16	–	1.5	Y	17	A
8	Kartal & Akatli 2016 [10]	5, M	T4-T7	LBP, constipation	1	NR	No	GTR	–	–	–		–	
9	Gong et al. 2015 [11]	39, F	C4-C6	L-UL pain	12	Yes	No	GTR	CTX, ANT, VCR	3800	36	Y	36	A
10	Lucic et al. 2015 [12]	19, M	C1	Neck pain	–	NR	No	STR	–	Yes	–		18	D
11	Zhao et al. 2014 [13]	15, M	L4-L5	R-LL pain	12	NR	No	GTR	CTX, AMD, IFO	5000	12	N	12	A
12	Mardekian et a. 2014 [14]	26, M	T12-L1	LBP	–	Yes	No	GTR	–	–	–		–	
13	Mardekian et a. 2014 [14]	70, M	T12-L1	LBP	–	Yes	No	STR	–	–	–		–	
14	Lozupone et al. 2014 [15]	44, F	L1-S3	Cauda equina	5	NR	No	GTR	VCR, ANT, CDDP, CAPE	4000	6	N	6	A
15	Bazzocchi et al. 2013 [16]	41, F	L4-L5	LL pain	–	NR	No	GTR	VCR, CTX, AMD, IFO, VP16	5400	31	Y	31	A
16	Pancucci et al. 2013 [17]	55, M	L4-S2	Cauda equina	–	Yes	Yes	GTR	ANT, IFO, VP16	5600	13	N	13	A
17	Pancucci et al. 2013 [17]	25, F	L2-L3	LBP	–	Yes	No	GTR	–	–	14	Y	14	A
18	Khalatbari et al. 2013 [18]	28, F	L5-S1	LBP	3	Yes	Yes	GTR	VCR, AMD, CTX, IFO, VP16	5000	72	N	72	A
19	Ellis et al. 2011 [19]	35, M	T12-L2	LBP	6	Yes	No	STR	–	–	2	N	2	A
20	Karikari et al. 2011 [20]	56, F	L1	LL pain	5	Yes	No	GTR	VCR, ADR, CTX, IFO, VP16	–	–		–	
21	Yan et al. 2011 [21]	10, M	C2-C3	Neck pain	0.5	NR	No	GTR	–	–	1	Y	1	D
22	Muzzafar et al. 2010 [22]	38, M	L1-S2	LL weakness	12	Yes	Yes	GTR	Yes (Drugs not specified)	–	1	N	1	A
23	Vincentelli et al. 2010 [23]	40, F	T11-L4	LL weakness	0.25	Yes	Yes	GTR	AMD, IFO	4000	6	N	6	A
24	Klimo et al. 2009 [24]	10, M	L4	R-LL pain	3	NR	No	STR	VCR, ADR, CTX, IFO, VP16	5040	12	N	12	A
25	Kim & Shin 2009 [25]	32, F	C3-C5	UL weakness	1.5	NR	No	STR	IFO, VP16	3000	12	N	12	A
26	Haresh et al. 2008 [26]	26, M	T11-S2	LL weakness	2	NR	No	GTR	VCR, AMD, CTX, IFO,CDDP, VP16	5000	2	Y	8	A
27	Mobley et al. 2006 [27]	32, M	L2-L4	LBP	7	Yes	Yes	GTR	DACT, VCR, AMD, CTX, IFO, VP16	5580	8	Y	12	D
28	Woestenborghs et al. 2005 [28]	11, M	C4-T2	UL, LL weakness	–	Yes	No	STR	VCR, IFO, AMD, VP16	–	–		–	
29	Uesaka et al. 2003 [29]	11, F	T1-T5	LL weakness	1	NR	Yes	STR	–	–	–		–	
30	Rock et al. 2002 [59]	61, F	L4-L5	L-LL pain	–	NR	No	GTR	CDDP, ADR, MTX, VCR	5000	48	Y	65	A

(*continued on next page*)

Table 2 (*continued*)

Case	Author	Age, Gender	Location	Chief presenting symptom(s)	Duration of any symptoms	Positive EWS-FL11 fusion transcript/Chromosome 22q12 translocation	Intratumoral hemorrhage	Initial treatment			Outcome after initial diagnosis (mo)			
								Surgery	Chemotherapy	Radiation (cGy)	PFS	Recurrence	OS	Status
31	Scantland 2018 [30]	14, F	L2-L3	LBP	6	Yes	Yes	GTR	VCR, AMD, CTX, IFO, VP16	5042	24	N	24	A
32	Hisaoka et al 1997 [31]	14, M	T12-L1	LBP	3	Yes	No	GTR	–	–	3	N	3	D
33	Bostelmann et al 2016 [9]	29, M	C6-C7	R UL pain	3	Yes	No	GTR	VCR, IFO, AMD, VP16	3600	1	Y	18	D
34	Isotalo et al 2000 [32]	52, M	L2-L5	LBP, LL weakness	6	NR	No	STR	–	1750	12	N	12	A
35	Duan et al 2010 [33]	25, M	L2-L3	LBP	–	No	No	–	6	5000	6	Y	6	A
36	Harimaya et al 2003 [34]	30, F	C2-C4	L UL numbness	–	NR	No	STR	VCR, AMD, IFO, DACT	5000	14	Y	14	D
37	Harimaya et al 2003 [34]	14, M	L1-L2	LBP	3	NR	No	GTR	VCR, AMD, IFO, DACT, CBDCA, IFO, VP16	None	67	N	67	A
38	Sahu et al 2010 [35]	11, M	L2-L3	LBP, LL weakness	–	NR	No	GTR	Yes (drugs not specified)	Dose NR	–	–	–	–
39	Fabre et al 2006 [36]	70, M	L4-S1	LBP	4	Yes	No	STR	AMD, IFO, VCR	3000	12	N	12	A
40	Kumar et al 2018 [37]	65, M	L2	LBP, LL weakness	–	NR	No	GTR	Yes (drugs not specified)	Dose NR	8	N	8	A
41	Akyuz et al 2004 [38]	31, F	L1-S1	LBP, LL weakness,	3	NR	No	STR	VCR, CCNU, CDDP	5280	2	Y	4	D
42	Kepes et al 1985 [39]	24, M	L4-L5	LBP	3	NR	No	GTR	None	4800	12	Y	18	D
43	Kepes et al 1985 [39]	56, M	L3	LL weakness	0.25	NR	No	GTR	None	4000	36	N	36	A
44	Kepes et al 1985 [39]	39, M	L5-S1	LL weakness	2	NR	No	STR	None	4000	30	Y	30	D

*Intraoperative bleeding.

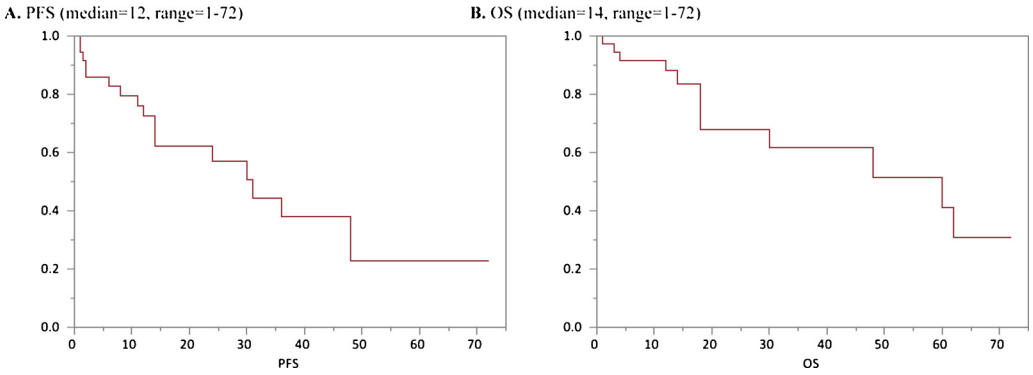

Fig. 2. Kaplan-Meier survival curves for **A.** PFS (n = 26) and **B.** OS (n = 27) for the overall PIEES cohort. PFS, progression free survival; OS, overall survival.

5. Conclusion

In summary, we provide an update on previously reported cases of PIEES from our institution along with a comprehensive review of published literature to summarize the clinical outcomes of this rare disease, characterized by poor overall survival. A combination of unique location, extraosseous nature and lack of defining imaging features are all clues to suspect a diagnosis of Ewing's sarcoma. Whenever possible, complete surgical resection should be pursued together with adjuvant chemotherapy and radiotherapy.

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Conflict of interest

No financial or other conflict of interest.

Ethical approval

Institutional Review Board (IRB) approval obtained.(IRB protocol: 15-000638, Neurosurgery Outcomes: Improving the Quality and Standards of Patient Care).

Informed consent

As all patient identifiers were removed, informed consent was deemed not necessary by our IRB.

Disclosures

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