Primary primitive neuroectodermal tumor of the lumbar extradural space

Case report

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Primary spinal primitive neuroectodermal tumors (PNETs) of the extradural space are very rare; only 10 cases have been reported in the English language literature. The histopathological diagnosis of primary spinal PNETs has been discussed for many years. These tumors have a rapidly progressive course, and there is no current consensus on the optimal therapeutic approach for these patients. The authors present a case of primary PNET located in the lumbar extradural space in a 13-year-old girl and report the clinical, radiological, histopathological, and surgical findings. They compare their findings with those from the other 10 cases reported in the literature and review relevant literature. (DOI: 10.3171/PED/2008/2/9/215)

KEY WORDS • extradural space • lumbar spine • primitive neuroectodermal tumor • spine • tumor

Primary neuroectodermal tumors are aggressive, poorly differentiated neoplasms in children and young adults.1,6,8,11,13,14,16,17,19,23,26,31 In the CNS, these tumors most frequently arise in the cerebellum of children and are called medulloblastoma.12 However, PNETs can also arise in the pineal gland, cerebrum, brainstem, and peripheral nerves.2,7,13,26,31 Primary spinal localizations (intramedullary, intradural–extramedullary, and extradural) are rare, with only 41 cases reported in the literature. Extradural locations are even more rare, and only 10 cases have been described.1,3,8,11,13,19,20,25,31,32 In this article, we present a young patient with a primary spinal extradural PNET, and we report the clinical, radiological, pathological, and surgical features. We also review the relevant literature.

Case Report

History and First Examination. This previously healthy 13-year-old girl presented with swelling on the left side of her low back as well as a 2-month duration of low-back pain radiating down to the left leg. She experienced lower-extremity weakness lasting 1 month before presentation. Physical examination confirmed the presence of an irregular mass, measuring ~4 × 4 cm in the left side of her low back. Neurological examination revealed Grade 4/5 motor power of the lower extremities bilaterally. The patellar reflexes were absent bilaterally. There was no bowel or bladder dysfunction. Lumbar MR imaging demonstrated the presence of a 60 × 53–mm extradural tumor with extraspinal extension at the left L2–3 level. The mass appeared iso-intense on T1-weighted images and hyperintense with homogeneous signal enhancement on T2-weighted images after the addition of Gd. The dural sac and conus medullaris were displaced contralaterally. This dumbbell-shaped tumor invaded the left paravertebral muscles via the neural foramen (Fig. 1).

First Operation. We performed a left L2–3 hemilaminectomy. Intraoperatively, the extradurally located gray-reddish soft tumor was poorly demarcated. The tumor appeared diffuse and bled on palpation. Through a laminectomy, the extradural tumor was completely removed and the paraspinal tumor infiltration was resected.

Histopathological Examination. Light microscopic examination of H & E–stained slides revealed layers of small, round, monomorphic cells with Homer–Wright rosette formation and hyperchromatic nuclei (Fig. 2). The mitotic rate

Abbreviations used in this paper: CNS = central nervous system; cPNET = central primitive neuroectodermal tumor; NSE = neuron-specific enolase; pPNET = peripheral PNET.
was high; results of PAS staining showed a focal intracellular glycogen. Immunohistochemical studies demonstrated a positive reaction for NSE, synaptophysin, and S100 protein, as well as small tumor areas immunoreactive for CD99 (MIC2) (Fig. 3). Light microscopic and immunohistochemical findings led to a diagnosis of a PNET.

First Postoperative Course. The postoperative period was uneventful. Following surgery, the patient’s condition improved gradually. A brain MR image, CT study of the thoracoabdominal region, and 99mTc bone scintigraphy revealed normal findings. Workup for metastases was negative. The lesion was classified as a primary extradural PNET because of the absence of a primary intracranial tumor, especially in the posterior fossa. A postoperative MR image of the lumbar spine revealed no residual tumor. Radiotherapy was planned but could not be performed because of the bureaucratic and social handicaps in our country. The patient was given 4 cycles of chemotherapy with etoposide (150 mg/m²/day), vincristine (1.5 mg/m²/day), adriamycin (20 mg/m²/day), ifosfamide (2000 mg/m²/day), and actinomycin-d (0.5 mg/m²/day). A postoperative MR image was obtained 2 months later and revealed no tumor recurrence in the lumbar region.

Second Presentation. Eleven months after surgery, the patient presented with flaccid paraplegia and urinary retention. Lumbar MR imaging showed an extradural L-1 mass with involvement all around the dural sac as well as L-3 vertebral collapse with dural sac compression. Conus medullaris compression was noted (Fig. 4A–C). Subsequently, a second workup was carried out, and thoracoabdominal CT scanning and cervical and thoracic spine and brain MR imaging did not reveal any abnormalities.

Second Operation. During the second surgery, an L-3 corpectomy with subtotal resection of the extradural tumor, iliac crest bone grafting, and spinal stabilization placed at the L2–4 level through a left anterolateral retroperitoneal approach were performed (Fig. 4D). An L-1 total laminectomy and subtotal resection of the extradural tumor with posterior approach were performed in the same operation.

Second Postoperative Course. The tumor’s histopathological and immunohistochemical phenotype did not change.
Radiotherapy was proposed, but the patient’s parents refused. In the days following the second operation, the neurological status of the patient was stable; she continued to have complete flaccid paraplegia and urinary retention. The patient died of aggressive local spread of the disease 14 months after primary diagnosis.

Discussion

Primitive neuroectodermal tumors, a group of malignant neoplasms, arise from pluripotent neural crest cells. These tumors are composed largely of undifferentiated neuroepithelial cells in subependymal zones. Histopathologically they are poorly differentiated, small, round blue cell tumors. The original nomenclature of these tumors was based on location and/or differentiation. Primitive neuroepithelial cells can persist in any part of the CNS, which may explain the presence of PNETs in locations other than the cerebellum. The World Health Organization 2000 classification grouped these tumors into the category of embryonal tumors composed of undifferentiated or less differentiated neuroepithelial cells, which have the capacity of differentiation to astrocytes, ependymal cells, melanocytes, or muscle cells. These tumors were termed “supratentorial primitive neuroectodermal tumors.” To include similar tumors located in the brainstem and spinal cord, the more general term PNET is recommended. Given that this designation is also used for similar but not identical tumors at extracerebral sites, the 2007 World Health Organization Working Group proposes to add the prefix CNS to these entities to avoid any confusion. The term “CNS PNET not otherwise specified” is synonymous with the current term “supratentorial PNET” as used for undifferentiated or poorly differentiated embryonal tumors that occur at any extracerebellar site in the CNS.

Most cases of PNET involving the spinal cord are drop metastases from primary intracranial tumors. A primary intraspinal PNET is rare, and only 41 cases have been reported in the English-language literature. These tumors may originate in the extra- or intradural spaces, with a predilection for the cauda equina. This might be due to the fact that the cauda equina is the portion of the peripheral nervous system in which the axons have become dependent on Schwann cells for the maintenance of their myelin sheaths. Before the diagnosis of a primary spinal PNET can be confirmed, the more common drop metastases of intracranial origin must be excluded. Our patient harbored a true primary spinal extradural PNET considering that repeated brain and spine MR imaging did not reveal any evidence of a cerebral primary tumor. Also, the extradural localization makes it unlikely that the tumor was a drop metastasis.

Primary spinal extradural PNETs are extremely rare. The 10 cases reported in the literature are summarized in Table 1. The intramedullary tumor may have originated from the spinal cord, and the primary spinal extradural tumor may have arisen from vertebrae, soft tissue, or spinal nerve roots, which belonged to peripheral PNET. These tumors tend to occur in young adults and children. Of the patients reported on in the literature, 8 were males and 2 were females. The age of manifestation ranged from 4 to 27 years, with an average of 16 years. The age of our patient was similar to those of the patients in the previously reported 10 cases of primary spinal extradural PNET. Extradural localization of spinal PNET is more frequent in children and young adults, whereas intradural–extramedullary or intramedullary localizations are more common in adults. The tumor involved the lumbar spine in 3 patients each, and the cervical spine, the cervicothoracic spine, the lumbosacral spine, and the sacral spine in 1 patient each. Similar to our patient, only 1 patient in the literature had a spinal PNET arising from the extradural space in the lumbar region with dural sac compression and extension into the paravertebral muscles. Also, there were 2 patients who had an extradural and paravertebral dumbbell tumor at the cervicothoracic (C6–T3) and cervical (C2–4) spine.

The duration of symptoms was variable (range 9 days–4 months). The clinical presentations were low-back pain, radiating leg pain, cervicothoracic pain, cervical pain, and spinal stabilization at L2–4 with Kaneda system via a left anterolateral retroperitoneal approach.

Fig. 4. Follow-up MR images 11 months after the first operation (A–C) and a radiograph obtained after the second operation (D). A: Sagittal T2-weighted image showing the collapsed L-3 vertebral body with dural sac compression and hypointense extradural tumor at L-1. B: Axial T1-weighted image showing an extradural L-1 mass with involvement all around the dural sac. C: Axial T1-weighted image showing vertebral collapse of L-3 with extradural involvement and infiltration of left anterior area from the tumor. D: Anteroposterior lumbar radiograph showing an iliac crest bone graft and spinal stabilization at L2–4 with Kaneda system via a left anterolateral retroperitoneal approach.
and urinary or bowel dysfunction. Our patient presented with weakness in the legs, low-back pain, left leg pain, and swelling on the left side of her lower back. Ours is the first patient to have been reported as presenting with a rapidly enlarging mass in the lower back.

All 10 patients underwent surgery; total tumor removal was performed in 1,3,8,11,13,19 and subtotal tumor removal in 2,11,13. Partial tumor resection was performed in 1 case because the major part of the tumor was in the mediatinum. In the other case, the authors reported that part of the tumor in the spinal canal was removed completely, but it encroached upon the L-5 vertebral body; therefore, both sides of the L-5 vertebra were carefully scraped. Postoperatively, only 2 patients underwent radiotherapy,20,31 and 7 patients underwent radiotherapy and chemotherapy,1,3,8,11,13,25,32 One patient did not receive postoperative radiotherapy and chemotherapy for financial reasons. Our patient underwent multigagent chemotherapy alone after resection. Radiotherapy was planned for the patient after the first operation but was not performed because of the bureaucratic and social handicaps in our country. Radiotherapy was again proposed after the second operation, but the patient’s parents refused.

Distant tumor metastasis occurred in 3 cases in the literature.11,13,25 One patient died of adjacent level vertebral tumor recurrence and lung metastasis.13 The second patient died of multiple lung metastases even though a recurrent tumor was not noted.11 The tumor presentation in the third patient was metastatic with pulmonary and mesenteric lymph nodes.25 One patient suffered local tumor recurrence in the cervical spine.19 Although no bone invasion was evident at the operation, she presented with a recurrent tumor in the L-1 extradural space and L-3 vertebral collapse (Fig. 4A–C). Pretreatment and follow-up workup studies did not reveal signs of distant metastasis. Of the 9 patients in the literature with available follow-up data, 2 died after an average of 18 months11,17 and 7 were alive at 25 months.1,8,19,20,25,31,32 The duration of survival was not documented in 1 patient.3 Primitive neuroectodermal tumors are classified as small, round cell tumors and must be distinguished from similar tumors that include the extraskeletal form of Ewing sarcoma, lymphoma, rhabdomyosarcoma, undifferentiated small cell carcinoma, and small round cell tumor of thoracopulmonary origin (Aksin tumor).1,7,8,14,25 It is still not clear whether the cell of origin is an internal granule cell of the cerebellum or an undifferentiated cell common to all portions of the nervous system.19 Primitive neuroectodermal tumors are undifferentiated neoplasms characterized by small, uniform, round cells with hyperchromatic nuclei and show evidence of neural differentiation, which typically forms Homer–Wright rosettes.1,7,8,13,14,16,17,23,26,28 The presence of these Homer–Wright rosettes and the expression of ≥2 different neural immunohistochemical markers (that is, NSE, S100 protein, synaptophysin, chromogranin A, neurofilament proteins, and Leu 7) is required to diagnose a pPNET.1,7,8,13,14,25,28 Intracellular glycogen can often be demonstrated by PAS staining in pPNETs, and the presence of intracellular glycogen favors the diagnosis of pPNET.1,5,36 Kumar et al.19 reported 3 cases of primary spinal pPNET and described the following pathological characteristics: 1) poorly differentiated small round/spindle-shaped cells; 2) cells either densely packed or placed in sheets or nests; 3) cells generally positive for neuronal markers like NSE (They could be a precursor of intermediate filaments like nestin, vimentin, or microfilaments; synaptophysin or glial fibrillary acidic protein may be positive depending on the differentiation of the cells; S100 is also commonly positive, and 4) cells may not stain positively for any analyses (in cases of undifferentiated cells). Although cPNETs and pPNETs are histologically similar, cPNET (medulloblastoma) and pPNET are distinct diseases with different clinical, immunohistochemical, and genetic profiles. Central PNET is associated with a different spectrum of cytogenetic abnormalities such as isochromosome 17q and specific regions on chromosome 1, and 8p, 1q, 11p, and 16q.31 Cytogenetic analysis detected the presence of a reciprocal translocation t(11;22)(q24;q12) in pPNET and Ewing sarcoma with up to 95% frequency, which was not detected in

<table>
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<th>Authors &amp; Year</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Duration (mos)</th>
<th>Level</th>
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<th>Additional Treatment</th>
<th>Metastasis</th>
<th>Recurrence</th>
<th>Survival (mos)</th>
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<td>26</td>
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<td>15 days</td>
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<td>none</td>
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<tr>
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<td>M</td>
<td>4</td>
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<td>complete</td>
<td>RT &amp; chemo</td>
<td>none</td>
<td>alive at 23</td>
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<tr>
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<td>M</td>
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<td>—</td>
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* chemo = chemotherapy; RT = radiotherapy; — = not documented.
Peripheral PNET and Ewing sarcoma share expression of the same oncogenes, including c-myc, c-myb, c-ets-1, and N-myc. The expression of CD99 (MIC2 glycoprotein), which can be detected by immunohistochemical staining, shows that specific chimeric genes of EWS-FLI1 are highly specific for pPNET. The CD99 antigen is the product of the MIC2 gene on the X and Y chromosomes. The positivity for CD99 defines this tumor as a peripheral rather than a CNS/supratentorial PNET. A pPNET was excluded because staining with CD99 remained negative. A pPNET is known to metastasize (bone, lung, liver, and lymph nodes) and invade tissues, whereas a pPNET rarely metastasizes outside the CNS. Peripheral PNETs and Ewing sarcomas have been grouped in the same category (Ewing sarcoma family), because of the same chimeric gene EWS-FLI1 and similar tumor expression of the glycoprotein CD99. The most frequent sites of occurrence are the chest wall, lower extremities, trunk, kidney, and orbit; however, pPNET and Ewing sarcoma rarely originate from around the spine. Peripheral PNETs and Ewing sarcomas are believed to derive from a primitive pluripotent cell from the neural crest, differing only in their stage of neural differentiation. The undifferentiated Ewing sarcoma is associated with a slightly better outcome, whereas an increasing degree of neuroectodermal differentiation has been associated with a poor prognosis. Differential diagnosis of pPNET and Ewing sarcoma is based on recognition of neural differentiation in pPNET, characterized histologically by the presence of Homer-Wright rosettes and immunohistochemically by expression of ≥ 2 different neural markers.

Histopathological analyses conducted in the 10 cases of primary spinal extradural PNETs reported in the literature revealed the following: mitosis in 3 cases, necrosis in 2, and Homer–Wright rosettes in 5. Immunohistochemical findings were positive for NSE in 6 cases, for S100 protein in 3, and positive for CD99 antigen in 4 cases. Only 2 groups of authors confirmed the presence of poorly differentiated small round cells with electron microscopy. Electron microscopic examination revealed some dense core neurosecretory granules, interdigitating cell processes, microtubules and intermediate filaments in the tumor cells. Only 1 group performed genetic analysis. Although we did not perform a chromosomal analysis for detection of EWS-FLI1 and electron microscopic examination in our patient, the light microscopic and immunohistochemical studies revealed a diagnosis of pPNET (small round cells; hyperchromatic nuclei; and well-defined Homer-Wright rosettes) and focal intracellular glycogen; positive reaction with NSE, S100 protein, and synaptophysin; and positive expression of the CD99 antigen.

Histologically and immunohistochemically, other small round cell malignancies, including malignant lymphoma, rhabdomyosarcoma, neuroblastoma, and synovial sarcoma were ruled out in our patient. The reported CT findings of pPNET are most commonly noncalcified soft-tissue masses with variable enhancement on contrast-enhanced images. Occasionally, cystic or necrotic areas are seen within the mass. On MR images, a pPNET appears generally isointense compared with muscle on T1-weighted images and heterogeneously hyperintense on T2-weighted images. Gadolinium enhancement is homogeneous and intense. The tumor presentation in 1 patient was bone destruction with vertebral collapse in this primary spinal extradural PNET literature review. The MR imaging findings in our patient were similar to those of previous reports of primary spinal extradural PNET; however, these imaging findings are nonspecific.

Intraspinal tumors are relatively rare in childhood. They are located in the epidural space in ~ 35% of cases, and they are most commonly neuroblastoma, followed by Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma. The differential diagnosis of extradural tumors other than primary spinal extradural PNETs includes primary or metastatic tumors (extraskeletal Ewing sarcoma, lymphoma, leukemic infiltration, plasmocytoma, and sarcoma) and rare benign extradural tumors. Given that the imaging findings of these extradural tumors are similar to each other, it is difficult to distinguish them before surgery. Benign extradural tumors such as schwannoma, meningioma, and hemangioma are relatively rare; they differ from extradural tumors with respect to their smooth tumor margin and lack of infiltrative growth pattern, suggesting benign tumors, and rather typical MR imaging signal characteristics in some selected cases. Differential diagnostic considerations regarding the intraspinal localization, such as meningioma, schwannoma, neurofibroma, and ependymoma are easily made during routine histological examination. Because MR and CT myelography are sensitive but not specific in detecting PNETs, a broad differential diagnosis must be considered when working up an intraspinal, extradural, well-demarcated mass.

The optimal treatment for primary spinal extradural PNET is uncertain. Initial treatment is total tumor removal whenever feasible. All patients reported on in the literature (as well as ours) underwent surgery for initial treatment, with total tumor removal in 9 cases and subtotal tumor removal in 2. However, the details of surgical findings were not well documented in the literature. Three groups of authors reported that hypervascularity, extending to the paravertebral muscles, invasion into spinal nerves, poor demarcation, and bone destruction with or without local recurrence are important surgical findings in primary spinal extradural PNET. The surgical findings after both surgeries in our patient were similar to these reports. Two groups reported that the tumor was soft, reddish, gelatinous, unencapsulated, well demarcated, and did not invade surrounding tissues. One group reported that partial tumor resection was performed because the major part of the tumor was within the mediastinum. The other group reported that the part of the tumor in the spinal canal was removed completely, but the L-5 vertebral body was encroached upon and both sides of the L-5 vertebra were carefully scraped. Partially resected tumors seem to be associated with a greater incidence of distant metastasis. Local recurrences may be seen in patients who have undergone total tumor resection, as happened in our case. In reviewing the literature, some reports described diffuse tumor infiltration and fixation to the spinal nerves, allowing for only partial tumor resection. Some authors have suggested that a tissue diagnosis with CT-guided biopsy and a screening evaluation should be completed before attempting a tumor excision to avoid cutting through an unexpected or undiagnosed tumor.

Postoperatively, only 2 patients underwent radiothera-


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One patient was treated using vincristine, Adriamycin, ifosfamide, and actinomycin-D for 4 cycles. Concomitant to the fourth chemotherapy cycle, radiotherapy was given. Another patient was treated with vincristine, Adriamycin, ifosfamide, and actinomycin-D with radiotherapy, but the cycles of chemotherapy were not reported. One patient was treated with vincristine, Adriamycin-D, and cyclophosphamide for 8 cycles with proton-beam radiation therapy combined with radiotherapy. One patient was treated with cyclophosphamide, pirarubicin, cisplatin, and etoposide with radiotherapy. In this patient chemotherapy was undertaken 14 times during 3 years. One patient was treated using vincristine, doxorubicin, and cyclophosphamide with mesna for 4 months. This patient then underwent 5 weeks of radiotherapy to the sacrum followed by an additional 4 months of chemotherapy. Another patient was treated using cytoxan, Adriamycin, and Vincristine, followed by radiotherapy. The cycles of chemotherapy were not reported in this patient. Chemotherapy and radiotherapy were repeated after metastasis, but the chemotherapeutic agents were not reported. We used 4 cycles of etoposide, vincristine, Adriamycin, ifosfamide, and actinomycin-D, which is used in the treatment of Ewing sarcoma.

Chemotherapy is now standard treatment in most protocols for children with infratentorial cPNET either prior to or following radiotherapy. The role of chemotherapy is unclear, because of the paucity of reports of patients with primary spinal extradural PNET. Furthermore, some authors reported the efficacy of high-dose chemotherapy combined with peripheral blood stem cell transplantation for patients with pPNET. Although all previously reported patients with primary spinal extradural PNETs underwent radiotherapy as part of their primary therapy, details of radiotherapy were not well documented. Only 5 authors reported the radiotherapy doses. One patient was treated using 30 Gy and multipotent chemotherapy. One patient was treated first with spinal axis segment irradiation using spot-scanning proton beam-radiation therapy combined with conventional craniospinal axis radiotherapy (total dose 36 Gy) and chemotherapy. Another patient was treated with 36 Gy of local radiotherapy with multagent chemotherapy. One patient underwent hyperfractionated radiotherapy (49 Gy in 18 days) to the tumor region during the fourth chemotherapy cycle. One patient was treated with 50 Gy to the tumor region and multipotent chemotherapy. Chemotherapy and radiotherapy were carried out again after metastasis, but the radiation dose was not reported. Doses of 24–36 Gy to the craniospinal axis with focal boosts in patients with cPNET are sufficient to provide control, but ≥ 40 Gy is required for local control in patients with pPNET. The accepted dose for local radiation in the spinal canal is 50 Gy. The role of radiotherapy is unclear because few cases of primary spinal extradural PNETs have been described.

The prognosis of primary spinal PNET (intramedullary, intradural–extramedullary, extradural) is poor; 63% of patients died within 36 months (survival information regarding 9 of 41 patients with primary spinal pPNETs was not documented). Of the 10 patients with primary spinal extradural PNETs, 2 died after a mean of 18 months and 7 were alive at 25 months. Survival was not documented in 1 patient. One group reported that their patient was free of recurrence at 6 years and 4 months. A possible explanation for this is that there is a better chance of initial total tumor removal in extradurally located spinal PNETs. However, the follow-up periods for patients who survived were short, and more prospective follow-up periods are needed. Our patient died of aggressive local spread of the disease 14 months after primary diagnosis. Even after multimodal treatment, the prognosis for patients with primary spinal extradural PNETs is poor. Early total tumor resection followed by radiotherapy and chemotherapy is recommended for these patients. Peripheral blood stem cell transplantation is a possible treatment for high-risk patients in whom multipotent chemotherapy is required. Future therapeutic regimens for primary spinal PNET include adjuvant therapy such as cytokines, interferon-γ, and tumor necrosis factor-α.

Conclusions

Primary spinal extradural PNET is very rare. Extradural localization of primary spinal PNETs occurs more frequently in children and young adults, whereas intradural–extramedullary or intramedullary localizations are more common in adults. This tumor should be included in the differential diagnosis of extradural mass lesions, especially in children and young adults. The treatment of this tumor is very difficult. Unfortunately, even with therapy, the prognosis is poor. The small tumor size, tumor extension, dumbbell tumor shape, wide resection, and the presence of recurrence or metastasis are the main significant prognostic factors in primary spinal extradural PNET. Special consideration must be given to this tumor in the extradural space. Resection, radiotherapy, and multipotent chemotherapy are the preferred treatment options for these patients. Clinical outcomes still need to be evaluated in prospective trials.

References

Primary PNET of the lumbar extradural space


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