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CASE REPORT

Dumbbell-shaped peripheral primitive neuroectodermal tumor of the spine—case report and review of the literature

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Abstract Primary spinal peripheral primitive neuroectodermal tumors (pPNETs) are extremely rare. Here, we present a case study of a 29-year-old male with a dumbbell-shaped pPNET at the T9-10 spine level, including details of his examination, surgical procedures applied, histological and genetic findings, and his subsequent treatment. We discuss the clinical course, the pathology and treatment for this disease, the surgical approach to thoracic dumbbell tumors and we review the literature. To our knowledge, this is the first report of a case of a dumbbell-shaped intradural and spinal peripheral PNET.

Keywords Peripheral primitive neuroectodermal tumor · Dumbbell tumor · Spinal tumor · Spinal surgery

Introduction

Primitive neuroectodermal tumors (PNETs) are rare aggressive neoplasms that are usually diagnosed in children and young adults. The PNET concept was originally applied to tumors arising in the central nervous system (CNS), which were termed central PNETs (cPNETs) [1]. The concept was later expanded to include non-CNS tumors derived from the neural crest, which were referred to as peripheral PNETs (pPNETs) [2]. Primary intraspinal PNETs can arise as intramedullary, extramedullary or extradural tumors at any level of the spine [3, 4].

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Case report

Examination

The 29-year-old man presented to the Olomouc Faculty Hospital in September 2006, after experiencing a three-month history of progressive back pain, followed by recent sudden onset of paraparesis and urinary incontinence. A neurological examination revealed a bilateral weakness of the lower extremities and numbness was detected below the T9 level.

Emergency magnetic resonance imaging (MRI) of the thoracolumbar spine, using gadolinium enhancement, showed a right-sided dumbbell-shaped intra-extraspinal tumor at the T9-10 level. A 5-cm-long intraspinal section of the tumor was compressing the spinal cord, but there was no enlargement of the right lateral recess and neural foramen. The lesion was well circumscribed; its signal was homogenous with strong enhancement (Fig. 1). Radiological findings relating to the tumor were suggestive of neurinoma. Brain MRI produced normal results.

Operation and postoperative course

An emergency T9-10 total laminectomy was performed under general anesthesia. A reddish-gray tumor of soft consistency was found in the intradural extramedullary space, and the tumor margin appeared to be well demarcated. Using an operating microscope, total resection of the intraspinal and right intraforaminal mass was achieved.

Positron Emission Tomography/Computed Tomography (PET/CT) of the whole body revealed the presence of a right paravertebral tumor at T10, but no evidence of an intraspinal mass (Fig. 2) and there was no indication of additional intraspinal lesions. A lateral extrapleural

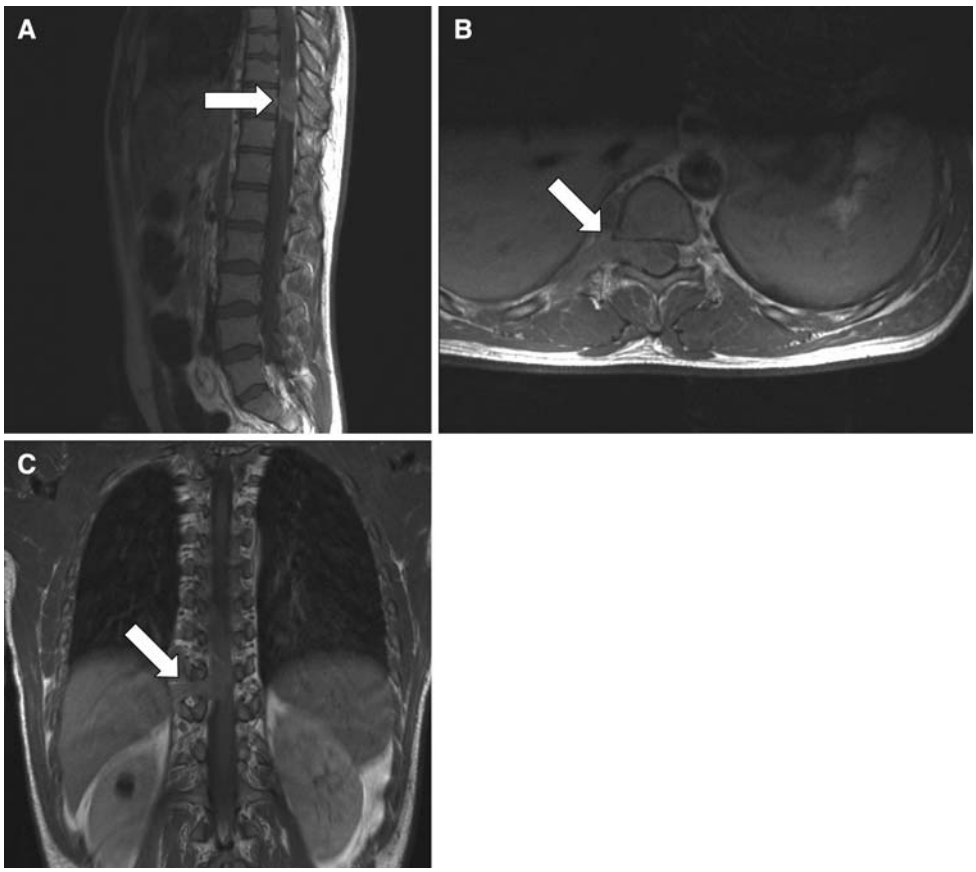

Fig. 1 Sagital T1-weighted contrast enhanced MRI (A), axial T1-weighted MRI (B) and coronal T1-weighted MRI (C) reveal a right-sided dumbbell-shaped intra-extraspinal tumor at the T9-10 level, compressing the spinal cord

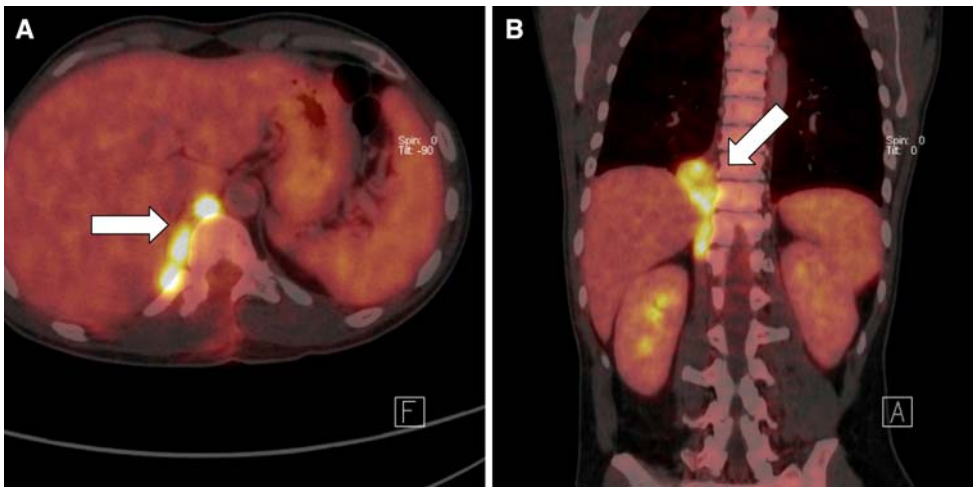

Fig. 2 Axial PET/CT scan (**a**) and coronal PET/CT scan (**b**) of the whole body after the first operation showed a right paravertebral tumor T10 with no evidence of an intraspinal mass and no indication of additional intraspinal lesions

approach with costo-transversectomy via the right 9th and 10th ribs was undertaken and a partial resection of the extraspinal mass of the residual dumbbell tumor was achieved. The resection was only partial, because surgery revealed extensive progression and poor demarcation of the tumor, so radical removal was already impossible.

The patient did not experience notable immediate postoperative complications. His clinical status, especially bilateral leg weakness and sensory loss in the lower extremities, slowly improved but back pain and bladder dysfunction remained.

Histological and genetic findings

Light microscopic histological examination of hematoxylin–eosin stained slides showed a cellular tumor composed

mainly of small round undifferentiated cells with high mitotic activity and necroses. No well-defined Homer–Wright rosettes were found.

Immunohistochemistry using anti-MIB-1 (Ki 67) antibodies revealed a high proliferative index (80%). Further staining revealed strong positivity of vimentin, EMA (Epithelial Membranous Antigen), NSE (Neuron Specific Enolase), CD99 (MIC2)—Fig. 3a, and focal positivity of GFAP. EGFR and p16 expressions were negative and 15% of tumor cells exhibited nuclear positivity of p53 (DO7 antibody). The diagnosis of undifferentiated high-grade PNET was based mainly on the basis of the histological and immunohistochemical findings.

Gene/locus/chromosomal gains or losses were cytogenetically investigated by applying fluorescent in situ hybridization (FISH) probes (Genetica s.r.o., Prague, Czech Republic) to histologically confirmed paraffin-embedded tumor specimens. Thresholds for gene/locus/chromosome amplification/gain and deletion/loss were arbitrarily set at 20% of affected cells, with a minimum of 100 nuclei evaluated. Cytogenetic analysis revealed amplification/gain of the following genes/loci: 9p21 (CDKN2A, CDKN2B), MPO (17q23) and c-Myc. There were deletions/losses of: 1p36, 19q13 and 13q14 (RB1). The other investigated genes/loci/chromosomes—chromosome 10, 17p13 (p53), N-myc, 22q11, 9q34, 11q13 (CCND1), EWSR1 (22q12), and 12q13 (MDM2)—appeared to be unaffected.

Furthermore, gene rearrangements at the EWSR1 locus were detected using dual color break-apart FISH probes (Abbott, Prague, Czech Republic), thus supporting the diagnosis of highly malignant peripheral primitive neuroectodermal tumor (Fig. 3b).

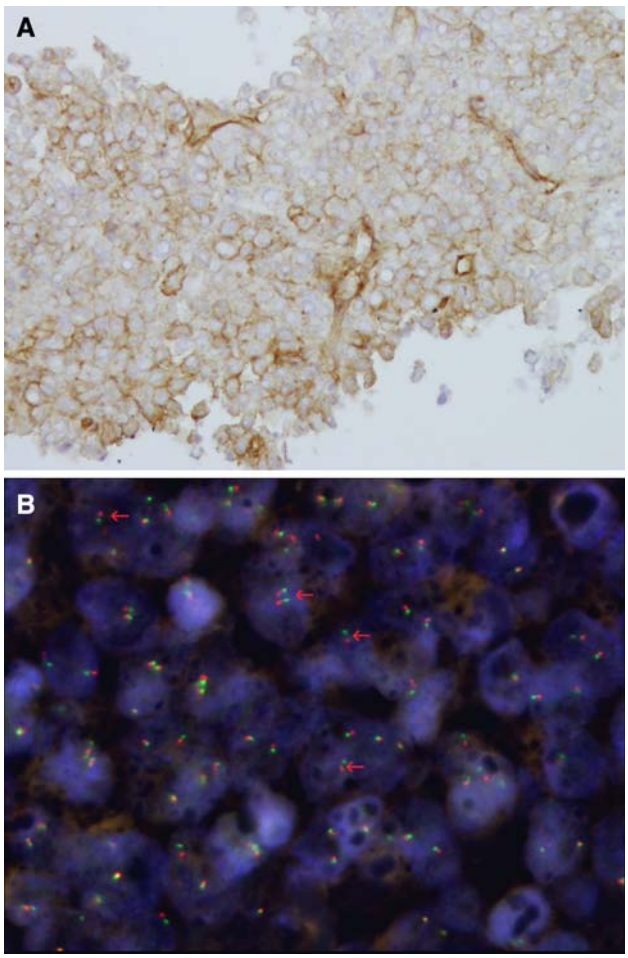

Fig. 3 Examples of immunohistochemical and cytogenetic examination of the tumor. **a** Cytoplasmatic membrane positivity of tumor cells for MIC2 glycoprotein (CD99). **b** Gene rearrangements at the EWSR1 locus (arrows) were detected in nuclei of tumor cells using dual color break-apart FISH probes (Abbott, Prague, Czech Republic). Both molecular findings support the diagnosis of a peripheral PNET

Post-surgical therapy

Since the tumor progressed rapidly, the patient was referred to a clinical oncologist and it was planned that he should undergo sandwich chemotherapy and radiotherapy according to the EURO-E.W.I.N.G. 99 protocol [5]. The treatment commenced with a four-agent combination chemotherapy (Vincristin, Ifosfamid, Doxorubicin, Etoposid). This treatment was repeated once every 3 weeks with excellent tolerance. However, after the second cycle, the patient was discharged and he died suddenly due to trombembolism complications four months after the pPNET diagnosis. Radiotherapy was not performed.

Discussion

The term primitive neuroectodermal tumor (PNET) was coined by Hart and Earle in 1973 [1]. In the third edition of the World Health Organization classification, PNETs are defined as embryonal tumors composed of undifferentiated or poorly differentiated neuroepithelial cells which have the capacity for or display divergent differentiation along neuronal astrocytic, ependymal, muscular or melanotic lines [6]. Whilst intracranial PNETs, particularly of the posterior cranial fossa, usually occur in children, PNETs with primary intraspinal location are mainly diagnosed in young adults [7]. Primary intraspinal PNETs are very rare and may originate in the extra- or intra-dural space, their preferred location is the cauda equina. The more common "drop" metastases of intracranial origin must be excluded for correct diagnosis [3, 8, 9].

Histologically, PNETs are poorly differentiated small round blue cell tumors. They have hyperchromatic nuclei and some neural differentiation, rarely exhibiting typical

Table 1 Review of publications relating to primary spinal PNETs

Reference	Age/Gender	Level	Location	Therapy	Survival (Months)	Spinal PNET
Smith [13]	24 y/M	L	Intradural-CE	S, RT	10	c PNET
Kosnik [14]	Less 10 y/n.a.	C	n.a.	S, RT, ChT	Less 12	c PNET
	Less 10 y/n.a.	C	n.a.	n.a.	Less 12	c PNET
	less 10 y/n.a.	TL	n.a.	n.a.	Less 12	c PNET
Kepes [15]	24 y/M	L	Intradural-CE	S, RT	18	c PNET
	56 y/M	L	Intradural-CE	S, RT	Alive at 36	c PNET
	39 y/M	L	Intradural-CE	S, RT	42	c PNET
Liu [9]	26 y/F	LS	Extradural	S, RT	Alive at 6	c PNET
Sevick [16]	26 y/M	C	Extramedullary	S, RT	36	c PNET
Jaksche [17]	15 y/F	TL	Intra-extramedullary	n.a.	18	c PNET
	26 y/M	TL	Intra-extramedullary	n.a.	36	c PNET
Freyer [18]	7 y/M	TL	Intramedullary	S, RT, ChT	20	c PNET
Ogasawara [19]	16 y/F	TL	Intramedullary	S, RT, ChT	29	c PNET
McDermott [20]	47 y/M	L	Intradural-CE	S, RT, ChT	16	c PNET
Kwon [21]	3 m/F	TL	Intramedullary	S, RT, ChT	n.a.	c PNET
Deme [3]	22 y/F	TL	Intramedullary	S	Alive at 15	c PNET
Hisaoka [22]	14 y/M	L	Intradural-CE	S	Alive at 3	p PNET
Papadatos [4]	23 y/M	T	Extramedullary	S, RT, ChT	Alive at 12	c PNET
Koot [23]	2 y/F	CC	Intra-extradural	S, RT	Several days	c PNET
Dorfmuller [8]	17 y/M	L	Extradural	S, RT, ChT	Alive at 23	p PNET
	32 y/M	Sa	Intra-extradural	S, RT, ChT	29	p PNET
Isotalo [24]	52 y/M	L	Intradurale-CE	S, RT	Alive at 12	p PNET
Mawrin [25]	69 y/M	T	Intra-extramedullary	S, RT	3	c PNET
Virani [26]	5 y/M	T	Intramedullary	S, RT	Alive at 8	c PNET
Yavuz [27]	18 y/F	LS	Intradural-CE	S, RT, ChT	Alive at 25	p PNET
Albrecht [7]	49 y/F	L	Intradural-CE	S, RT, ChT	23	p PNET
	29 y/F	TL	Intramedullary	S, RT, ChT	17	c PNET
Kim [28]	17 y/M	TL	Intra-extramedullary	S, RT	Alive at 4	p PNET
Aydin [29]	16 y/M	T	Extradural	n.a.	n.a.	c PNET
Akyuz [30]	31 y/F	LS	Intradural-CE	S, RT, ChT	8	p PNET
Weber [31]	26 y/M	TL	Extramedullary	S, RT, ChT	Alive at 17	p PNET
De Tommasi [32]	38 y/M	T	Intramedullary	S, ChT	18	c PNET
Fabre [33]	70 y/M	LS	Intradural-CE	S, RT, ChT	Alive at 12	p PNET
Kampman [12]	3 y/M	C	Intramedullary	S	1	c PNET
Jain [34]	54 y/F	C	Intramedullary	S, RT	n.a.	c PNET
Koudelová [35]	28 y/F	L	Extradural	S, RT, ChT	Alive at 24	p PNET
Nutman [36]	19 y/F	TL	Extramedullary	S, RT, ChT, ASCR	Alive at 24	p PNET
Perry [10]	27 y/M	L	Intradural-CE	S, RT, ChT	Alive at 72	p PNET
	16 y/F	L	Intradural-CE	S, RT, ChT	Alive at 5	p PNET
Feng [37]	24 y/M	T, TL	Extradural	S, RT	Alive 12	p PNET
Hrabálek	29 y/M	T	Extramedullary	S, ChT	4	p PNET

n.a. Not available, *y* Year, *m* Month, *M* Male gender, *F* Female gender, *CC* Cervicocranial, *C* Cervical, *T* Thoracic, *TL* Thoracolumbar, *L* Lumbar, *LS* Lumbosacral, *Sa* Sacral, *CE* Cauda equina, *S* Surgery, *RT* Radiotherapy, *ChT* Chemotherapy, *ASCR* Autologous stem cell rescue

Homer–Wright rosettes [10]. Nowadays, demonstration of MIC2 glycoprotein expression by immunocytochemical staining (CD99) aids in diagnosis. More recently, the discovery of a specific EWS-FLI1 chimeric gene, and the general identification of EWS1 gene rearrangements in pPNETs, offer reliable tools for diagnostically differentiating between cPNETs and pPNETs [11, 12].

Through a biomedical database search, we found 40 additional published cases of primary intraspinal PNETs, as listed in Table 1 [3, 4, 7–10, 12–37]. Including our case,

the age of manifestation ranged from 3 months to 70 years with an average age of 26 years. Twenty-four patients were males, 14 were females and in three cases no gender was specified. The tumor involved the cervical spine in six patients, the thoracic spine in seven patients, the thoracolumbar spine in 11 patients, the lumbar spine in 12 patients, the lumbosacral spine in four patients and the sacrum in one patient. Nine tumors were intramedullary located, four were partly intramedullary and partly extramedullary, four were intradurally and extramedullary, 13 were intradurally and involved the cauda equina, two were partly intradurally and partly extradurally, five were fully extradurally located and in three cases the location was not specified. However, our patient was the only one with extramedular and extraspinal localization of the mass of the tumor. Information on treatment was not available in five cases, all of the other 36 patients underwent surgery; postoperatively, 31 patients received radiation therapy and 20 patients received chemotherapy, including one who underwent high dose chemotherapy followed by autologous stem cell transplantation. Out of the 38 patients for whom follow-up data were available 21 died after an average of 17 months and 17 patients lived for 3–72 months. To date, 25 cases of spinal central PNET have been reported in the literature; our patient is the 16th reported case of spinal peripheral PNET.

Tumors with both intraspinal and anterior paraspinal components that communicate via an intervertebral foramen are defined as dumbbell tumors. The size and distribution of the tumor components varies considerably and probably reflects tumor origin and histology. Neurogenic tumors are the most common dumbbell tumors [38]. Hourglass (dumbbell) neurogenic tumors were identified and named by Heuer in 1929 [39]. They include nerve sheath tumors (schwannoma, neurofibroma), ganglioneuroma and neuroblastoma. Intraspinal meningeoma may rarely extend distally through the nerve root sleeve into the anterior paraspinal region [40]. Perineural or direct proximal extension of tumors arising in the anterior paraspinal region or adjacent visceral structures (e.g., lung, kidney) may also gain entrance to the spinal canal via an intervertebral foramen. These include: paraspinal sarcomas, which often extend through several foramina; hemopoietic neoplasms, such as lymphoma or solid leukemic infiltrates; and primary or secondary pulmonary or renal malignancies. In these tumors, the intraspinal component usually remains epidural. Thoracic meningoceles may also present as a dumbbell mass, but this is rare.

Liu et al. described the radiological features of the dumbbell shape of a PNET tumor in a 26-year-old woman with an extradural cPNET arising from the L5/S1 levels and extending into the pelvic cavity through the right sacral foramen [9]. Dorfmuller et al. presented a "club-like" homogeneous enlargement of the right S1 nerve root with concomitant enlargement of the lateral recess and neural foramen in a patient with an intra-extradural pPNET [8]. Similarly, Perry et al. described an intradural pPNET lesion in L4 and L5 which extended beyond the neural foramen into the extraforaminal space and Koudelová et al. presented an extradural pPNET in L1/2 with an extension bilaterally to the neural foramen [10, 35]. To our knowledge our patient is only the second case of a dumbbell-shaped spinal PNET reported in the literature and the first case of dumbbell-shaped intradural and peripheral PNET tumor.

Preoperative diagnosis of any intraspinal extension is essential for determining the optimal surgical approach [41]. MRI is currently the preferred diagnostic tool because it is able to accurately detect and describe any longitudinal extension of the spinal component of the tumor. Further, it helps to determine the anatomical classification (intramedullary, intradural and extramedullary, or extradural) [41, 42]. MRI is helpful despite the fact that there are no radiological criteria that can clearly differentiate a pPNET from other intraspinal tumors.

The surgical approach to the thoracic dumbbell tumors remains controversial and various surgical procedures, including single-stage, double-stage, anterior and posterior approaches, have been recommended [40, 41, 43–47]. Preoperative identification of intradural tumor extension is critical to operative planning because not all intraspinal dumbbell tumors, including many nerve sheath tumors, exhibit intradural extension. The intradural portion of the tumor can be safely removed with standard microsurgical techniques via laminectomy with direct visualization of the tumor/spinal cord interface and unambiguous identification of the nerve root attachment. A unilateral facetectomy and T-shaped lateral dural incision over the root sleeve provide contiguous exposure of the foraminal portion of the tumor once the spinal cord has been decompressed [40]. Sacrifice of the entire spinal nerve is usually required once the tumor extends distally to the dorsal root ganglia, especially for malignant tumors. Fortunately this rarely results in significant loss of motor functions [48]. Watertight dural repair, with a fascial patch if necessary, is performed after removal of the intradural and foraminal tumor components. Excessive removal of the mass may impair neurological function immediately after surgery as a result of intraoperative parenchymal injury. Thus, during the removal of the intraspinal portion of the tumor there is a risk of paraplegia or other sequelae due to spinal cord injury. In our patient we used an operating microscope to remove the intraspinal portion of the tumor with minimal damage to the adjacent structures. Special care was taken to avoid complete resection of the facet joints. Although spinal canal reconstruction was not required in our case, when

facet joint resection is needed a stabilization procedure should be performed [45]. The anterior paraspinal tumor component is removed subsequently, through the lateral portion of the exposure. Since this dissection remains entirely extrapleural, the risk of a postoperative CSF/pleural fistula is avoided. Although most paraspinal tumors are more effectively exposed through an extensive anterolateral or posterolateral thoracotomy, the lateral extracavitary (extrapleural) approach is associated with reduced morbidity and may be preferred in some patients. The lateral extracavitary approach is useful for large dumbbell tumors, where definitive or radical gross total resection is the appropriate surgical objective. This approach is ideal for large dumbbell tumors with substantial intradural and anterior paraspinal tumor components [40]. In general, spinal stability, tumor size and control over the adjacent visceral and vascular structures have conflicting requirements, thus affecting selection of the optimum surgical approach. In our case, a vertical midline incision and laminectomy was followed by an extended lateral incision and a costo-transversectomy provided sufficient exposure and orientation for extrapleural partial resectioning of the pPNET tumor.

The main purposes of surgery are to provide neurological improvement, improve the quality of life, allow early mobilization and achieve sufficient cytoreduction for further oncological management. Although the ideal surgical treatment of dumbbell malignant tumors, including PNETs, consists of total "en bloc" resection, this may be limited by the involvement of soft tissue and ribs. Although the potential role of radiotherapy and/or chemotherapy is debatable, in cases of incomplete resection and/or high probability of the occurrence of residual PNET tumor cells, tumor adjuvant therapy should be considered.

The prognosis of patients with pPNET has improved dramatically since the introduction of chemotherapy and radiation therapy. Radiotherapy better controls local disease, but without systemic chemotherapy patients are at a great risk of distant metastases. Chemotherapy may give new hope for the management of these tumors, especially in the early stages. As long as peripheral PNETs are histologically and molecularly linked to Ewing sarcomas, their therapeutic management may be considered in this field [35, 49, 50]. Radiotherapy is usually undertaken after three or four [49], or six [5], cycles of chemotherapy. It is important to note that despite the combination of surgery, radiotherapy and chemotherapy, the prognosis remains poor but increasing experience with this rare type of tumor is likely to improve the treatment strategy in the future [30].

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