J Neurooncol (2007) 81:259–264
DOI 10.1007/s11060-006-9178-1

CLINICAL–PATIENT STUDIES

Primary peripheral primitive neuroectodermal tumors of the spinal cord: report of two cases and review of the literature

R. Perry · I. Gonzales · J. Finlay · S. Zacharoulis

Received: 19 January 2006 / Accepted: 10 April 2006 / Published online: 3 January 2007

Abstract Primary intraspinal peripheral primitive neuroectodermal tumors (pPNETs) are extremely rare tumors with only seven reported cases in the literature. The histopathologic diagnosis of this tumor is complex and has led to a variety of treatment approaches. The distinction between central and peripheral type primary spinal cord PNETs has not always been made in the literature, leading to a paucity of data in this disease. We present here two young patients with primary intraspinal pPNET, their treatment and outcome. The first patient, a 27 year old male, presented with an intradural mass extending from L2 through L5, after multiple relapses, he is currently alive with disease after 72 months, the longest survival yet reported. The second patient, a 16 year old female, presented with an intradural mass at the cauda equina from L2 through L5, and is currently alive with responsive disease at 5 months after initial diagnosis. Here, we discuss the clinical course, the pathology and treatment for this disease and review the literature.

Keywords Peripheral primitive neuroectodermal tumors · Chemotherapy · Radiation therapy · Spinal cord tumors

R. Perry (✉) · J. Finlay · S. Zacharoulis
Department of Pediatric Hematology/Oncology Childrens Hospital Los Angeles, University of Southern California, Keck School of Medicine, 4650, Sunset #54, Los Angeles, CA 90027, USA
e-mail: perryr@email.chop.edu

I. Gonzales
Department of Pathology, Childrens Hospital Los Angeles, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

Introduction

Primitive neuroectodermal tumors (PNETs) are small round blue cell tumors that are relatively common in children and are mainly intracranial in location. Primary spinal PNET is a rare condition in adults and even more so in children. They can be either central (cPNET) or peripheral (pPNET) in origin. Central PNET are morphologically indistinguishable neoplasms from medulloblastoma, but are located elsewhere in the central nervous system (CNS) outside the posterior fossa. Peripheral PNETs are closely related to the Ewing's family of tumors (EFTs) [1–20]. Spinal pPNETs have poor survival rates and there is no current consensus on the best treatment approach to these patients. Surgical tumor resection is the cornerstone of therapy. The role of adjuvant treatment modalities is not well defined, due to the absence of prospective randomized trials for this extremely rare clinical entity. We present here two young patients with primary intraspinal pPNET, their treatment and outcome.

Patient 1

A previously healthy 27-year old male presented with 8 months of intermittent quadriceps muscle pain. An MRI of the spine showed a large lesion in the spinal canal from L4 through L5, which extended beyond the neural foramen into the extra-foraminal space. Brain MRI, chest CT, bone scan, bone marrow biopsy and CSF cytology revealed no evidence of metastatic disease. Laminectomy from L4 through L5 with gross total resection was performed. The patient

received seven cycles of chemotherapy with cyclophosphamide (2,100 mg/m^2/d) on days 1 and 2, and a 72-hour continuous infusion of doxorubicin (75 mg/m^2) and vincristine (2 mg/m^2) starting on day 1. Cycles 4, 5, and 7 consisted of five consecutive days of ifosfamide (1,800 mg/m^2/d) and etoposide (100 mg/m^2/d). He then received hyperfractionated focal radiation therapy to the L4 through L5 region, with a total dose of 45 Gy delivered over 21 days. Follow-up MRI scan of brain and total spine were negative for disease.

He remained disease free for 20 months after diagnosis. On routine disease re-assessment, an MRI scan revealed a new nodular focus of abnormal intrathecal enhancement posterior to L1 without metastases. He underwent gross total resection of the intradural lesion from L1 through L2. He was then treated with six cycles of cyclophosphamide (250 mg/m^2/dose) followed by topotecan (0.75 mg/m^2/dose), daily for 5 days, followed by focal radiation therapy (45 Gy). He subsequently underwent myeloablative chemotherapy, consisting of temozolomide (100 mg/m^2/dose) twice daily on days –10, –9, –8, –7, –6, followed by thiotepa 300 mg/m^2/d and carboplatin AUC 500 mg/m^2 on days –5, –4, –3 with autologous peripheral blood hematopoietic stem cell rescue (PBHSCR). His follow-up MRI scans of the brain and total spine were negative for disease.

Twenty-one months after his first relapse, the patient presented with lower back pain radiating bilaterally to the knees. He then began having difficulty urinating culminating in urinary retention. MRI scan showed a 2.9 cm circumscribed mass within the thecal sac from L5 through S1without other metastases. Gross total resection was performed. The patient had persistent lower extremity paresthesias post-operatively. He began daily etoposide (50 mg/m^2/day) for 21 days each month. Concurrently, he received focal irradiation with 21 Gy in 12 fractions over 19 days to L5 through S3 and an additional 23 Gy in 13 fractions to the sacrum. He then received continued chemotherapy with oral etoposide (100 mg/m^2/day) and temozolomide (90 mg/m^2/day) for 42 days repeated every 14 weeks, as well as daily oral celecoxib (200 mg bid), thalidomide (average dose 500 mg daily) and retinoic acid (100 mg/m^2/dose) twice daily for 14 days per month. He is currently 72 months from initial diagnosis. At the time this manuscript was prepared, he was found to have recurrent nodules at L1 through L2, 14 months after his last relapse. He underwent complete resection without further chemotherapy at this time secondary to a non-myelodysplastic anemia and thrombocytopenia.

Patient 2

The second patient is a previously healthy 16-year old female who presented with 3 months of lower back pain radiating bilaterally to the legs. Three weeks prior to diagnosis she developed paresthesias in both lower extremities with progressive weakness and was unable to ambulate. An MRI of the spine showed a gadolinium enhancing intradural, extramedullary tumor extending from L2 through S1 (Fig. 1). MRI of the brain, CT scan of the chest, abdomen and pelvis, bone scan and CSF cytology were all negative for metastatic disease. The patient underwent laminectomy from L2 through L5 with partial resection of a smooth, red-tan tumor.

She was treated with five cycles of cyclophosphamide (1,200 mg/m^2), liposomal doxorubicin (50 mg/m^2) and vincristine (2 mg/m^2) alternating with etoposide (100 mg/m^2) and ifosfamide (1,800 mg/m^2). She has also received focal radiation therapy to the L1

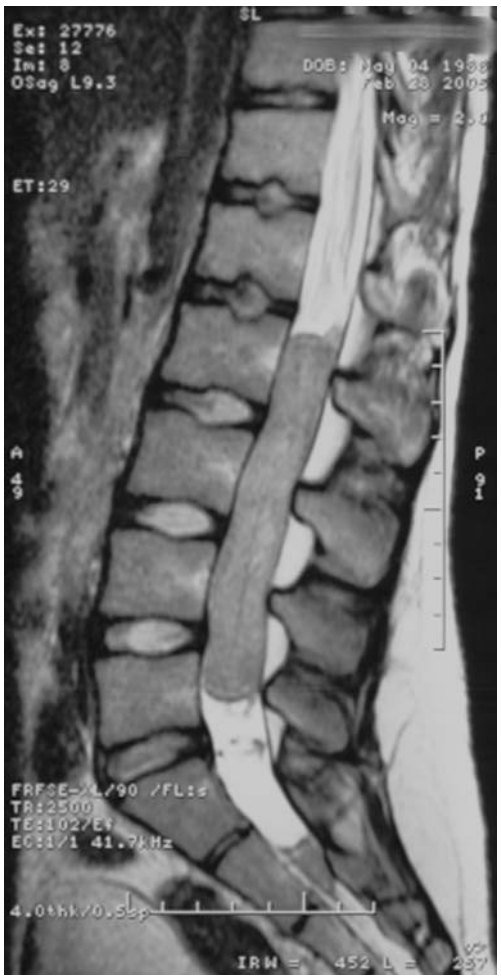

Fig. 1 Sagittal T2-weighted MRI scan revealing an intradural, extramedullary mass extending from L2 through S1 (patient 2)

through S2 region with a total does of 45 Gy delivered in 25 fractions. Disease re-assessment after five cycles of chemotherapy including MRI scan of total spine showed an interval decrease in the size and enhancement of the residual tumor in the cauda equina. She is currently alive with residual disease, responsive to ongoing chemotherapy, and with gradually improving neurologic function.

Pathology

Histopathological examination in both cases revealed similar findings. The tumors were highly cellular with diffuse and lobular growth patterns separated by thick fibrovascular septae. The tumors exhibited a bimodal cellular population of light and dark cells (Fig. 2). The former, which constitute most of the tumor cellularity, were rounded with moderate pale cytoplasm and an inconspicuous outer membrane. The nuclei were round to oval, centrally located, with finely granular chromatin and a delicate nuclear membrane. There were small nucleoli noted in scattered cells. The dark cells were dispersed and focally formed irregular aggregates amidst light cells. These tumor cells were angulated and had an irregular nucleus with dense chromatin and eosinophilic cytoplasm. There were scattered mitosis and individual cell necrosis. Immunohistochemistry disclosed a neural phenotype with positive staining for CD99 (Fig. 3) and PGP 9.5, with focal staining for synaptophysin and vimentin. There were also isolated tumor cells that stained positive for keratin. Desmin, tyrosine hydroxylase, GFAP and CD45 were negative. There was no evidence of significant epithelial or mesenchymal differentiation. In the second case, cytogenetic studies revealed a 46,XX,t(11;22)(q24;q12)/46,XX karyotype suggesting the presence of a translocation of t(11;22).

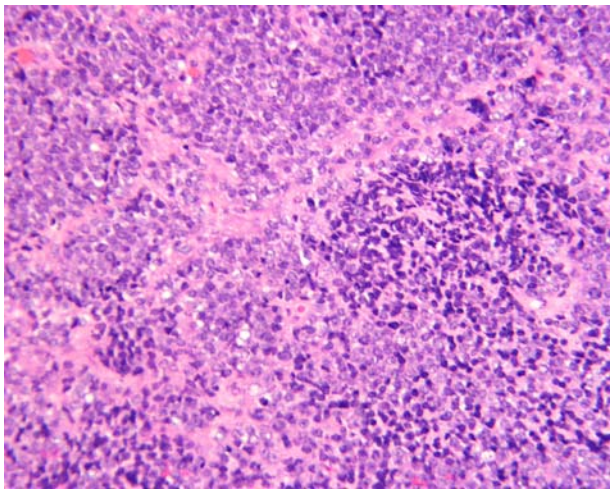

Fig. 2 Light microscopic photograph showing a typical highly cellular pPNET tumor consisting of undifferentiated small round cells with frequent mitoses

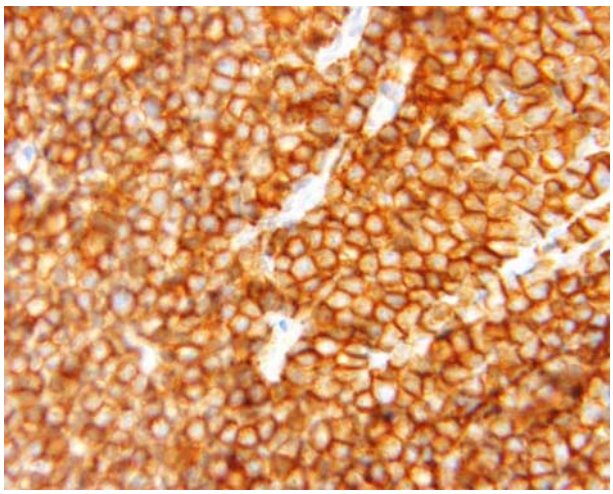

Fig. 3 CD 99 immunoreactivity in pPNET tumor cells (patient 2)

Discussion

Primary spinal PNET is a very rare tumor in both children and adults. Thirty patients with the diagnosis of ''primary spinal PNET'' have been reported in the literature [1–22]. These include patients with peripheral PNET (pPNET); however, the histopathologic distinction between central and peripheral PNET has not commonly been made in these reported cases. Histologically PNETs are poorly differentiated, small, round blue cell tumors. They have hyperchromatic nuclei and features of neural differentiation, rarely with typical Homer-Wright Rosettes [23]. The central PNET (cPNET) and pPNET are histologically similar however, cPNET is associated with a different spectrum of cytogenetic abnormalities (isochrosome 17q for example) [24]. Peripheral PNETs however, are closely related to Ewing's sarcoma and are part of the so-called EFTs [25, 26]. Strong immunoreactivity for mic-2 (CD99) and neuronal markers such as PGP 9.5, synaptophysin and neuron specific enolase strongly support the diagnosis of pPNET [27]. Only seven out of thirty of the previously reported cases of spinal PNET documented immunohistochemical staining for mic-2 (CD99) and where thus defined as ''primary spinal cord pPNETs''. Here we have reported two additional patients with primary spinal pPNET.

Primary spinal pPNETs have been reported in pediatric patients (3) and adults (6) with a median age of 30 years (range 16–52 years) including our 2 patients (Table 1) [2, 3, 7, 10, 20, 21]. There is a male

predominance with a male to female ratio of 2:1. Peripheral PNETs can be extramedullary or extradural tumors. Lumbar location is the most frequently encountered in four of nine reported cases. Their clinical presentation as well as the duration of symptoms can be variable. Metastatic disease at the time of diagnosis has not been described.

The long term prognosis of this disease and the most effective treatment remains unclear. In this review, we identified six patients that are survivors with very short follow up (median 22 months, range (4–72 months) [7, 10, 20, 25]. Our adult patient (patient 1) has the longest follow up (72 months) reported with this disease in the literature.

Treatments to date have included surgical resection, irradiation, and chemotherapy. The impact of the adjuvant therapeutic modalities can not be accurately delineated given the heterogeneity of regimens used in this small number of patients (Table 2). Gross total resection has been reported in five of nine recorded

Table 1 Summary of nine patients with primary intraspinal peripheral PNETs

Patient	Sex	Age (yr)	Level	Metastases	Treatment	Recurrence	Survival (Months)	Reference
1	M	32	Sacral	None	Gross total resection, RT: focal, CT: cisplatin + hyaluronidase	8 months later: local progression, Surgical Resection, RT: focal, CT: cisplatinum + hyaluronidase 4 months later: subarachnoid spread, local and cervico-thoracic spine metastases, RT: craniospinal, CT: VCR, Actinomycin D, Ifosfamide, and Doxorubicin	29	[7]
2	M	17	Lumbar	None	Gross total resection, CT: 4 cycles VCR, Actinomycin D, Ifosfamide, and Doxorubicin, RT: focal		Alive 23	[7]
3	M	52	Lumbo-sacral	None	Tumor Debulking, RT: craniospinal		Alive 12	[10]
4	F	49	Lumbar	None	Gross total resection, RT: focal, CT: VCR, cisplatinum, CCNU	17 months later local relapse resected, RT: focal, Thoracic metastasis. Palliative CT: gemcytabine.	23	[3]
5	F	31	Lumbo-sacral	None	Subtotal resection, RT: focal, CT: CCNU, cisplatin, VCR	6 months after diagnosis left frontoparietal mass was resected. Then 2 weeks later recurrence at original site	8	[2]
6	M	17	Thoraco-lumbar	None	Subtotal resection, RT: craniospinal		Alive 4	[21]
7	M	26	Thoraco-lumbar	None	Gross total resection	5 weeks later local extension. CT: VCR, Ifosfamide, Doxorubicin, VP-16, RT: Craniospinal, CT: VCR, Actinomycin, Cyclophosphamide	Alive 17	[20]
8	M	27	Lumbar	None	Gross total resection, RT: focal, CT: cyclophosphamide, VCR, Doxorubicin alternating with Ifosfamide and Etoposide	20 months later relapse. Gross total resection, RT: focal, CT: cyclophosphamide and topotecan with PBHSCR. 21 months later relapse. Gross total resection, RT: focal, CT: oral VP-16 and temozolamide. 14 months later cauda equina relapse, Gross total resection	Alive 72	Present case
9	F	16	Lumbar	None	Partial resection, RT: focal, CT: Cyclophosphamide, Doxorubicin, VCR alternating with Etoposide and Ifosfamide		Alive 5	Present case

CT, chemotherapy; RT, radiotherapy; PBHSCR, peripheral blood hematopoietic stem cell rescue; VCR, vincristine; CCNU, lomustine

Table 2 Adjuvant treatment modalities and outcome in patients reported in the literature with primary spinal pPNET

Adjuvant treatment	Number of patients treated	Number of patients alive
Craniospinal irradiation	2	2
Focal irradiation + chemotherapy	6	2

patients [2, 3, 7, 10, 20, 21]. When all the reported cases with ''primary spinal cord PNET'' are reviewed, 75% of the patients reported as having a gross total resection were alive at the time of report in comparison to 35% of the patients who had an incomplete resection [1–20]. The benefit of gross total resection in the nine reported patients with primary spinal cord pPNETs is less clear since three out of five patients with complete resection are survivors in comparison to three out of four patients who had an incomplete resection (Table 1).

Both focal and craniospinal irradiation of varying dosages have been used to treat patients with PNET. For patients with medulloblastoma/central PNET 24–36 Gy to the craniospinal axis with focal boosts are sufficient to provide control with excellent outcomes [28] whereas at least 40 Gy are required for local control in patients with pPNETs [29]. The two patients with primary spinal pPNET who received craniospinal irradiation at diagnosis (patients 3 and 6, Table 1) are survivors while one out of two that received craniospinal irradiation at the time of progression is also a survivor (patient 7, Table 1). The adequate doses and field of irradiation to provide control in this disease can not be established based on the current literature. Our patient who initially received 45 Gy as focal therapy, has experienced two out of field relapses and most recently an in field relapse. Both in field and out of field failures have also been common after irradiation according to the literature [1–20].

The role of chemotherapy is also unclear in this rare disease. Several chemotherapeutic regimens have been used in six of the nine reported patients with the diagnosis of primary spinal pPNET (Table 1). Interestingly, our patient with the longest follow up underwent myeloablative chemotherapy with autologous PBHSCR during the course of his treatment for a primary pPNET. Recently Barker et al. [30] reported that intensive chemotherapy followed by PBHSCR as consolidation therapy for patients with EFT in second remission is a potentially efficacious therapeutic modality. The Euro-Ewing's 99 study, which is currently ongoing, is evaluating the role of myeloablative chemotherapy with PBHCR for patients with EFTs and high-risk disease or lung metastases.

In conclusion, primary spinal pPNET is an exceedingly rare disease in both children and adults and has a still ill-defined prognosis over the long-term. It is essential to establish a distinction in diagnosis between a central and peripheral PNET of the spine, since the treatment should be tailored accordingly. Options of treatment would include gross total resection with acceptable morbidity. The selection of irradiation field should be determined with caution and it is not clear from the small number of patients reported in the literature whether all patients should receive craniospinal irradiation in addition to focal primary site irradiation, although it appears that there might be benefit to craniospinal irradiation when compared to focal irradiation and chemotherapy. The role of CSF cytology in assisting with this decision has not been evaluated. Myeloablative chemotherapy with autologous PBHSCR could be further explored in this particular subset of patients with spinal cord pPNET.

References

1. Kwon OK, Wang KC, Kim CJ, Kim IO, Chi JG, Cho BK (1996) Primary intramedullary spinal cord primitive neuroectodermal tumor with intracranial seeding in an infant. Childs Nerv Syst 12:633–636
2. Akyuz M, Demiral AN, Gurer IE, Ucar T, Tuncer R (2004) Primary primitive neuro-ectodermal tumor of cauda equina with intracranial seeding. Acta Neurochir (Wien) 146:525–528
3. Albrecht CF, Weiss E, Schulz-Schaeffer WJ, Albrecht T, Fauser S, Wickboldt J, Hess CF (2003) Primary intraspinal primitive neuroectodermal tumor: report of two cases and review of the literature. J Neurooncol 61:113–120
4. Albright AL, Wisoff JH, Zeltzer P, Boyett J, Rorke LB, Stanley P, Geyer JR, Milstein JM (1995) Prognostic factors in children with supratentorial (nonpineal) primitive neuroectodermal tumors. A neurosurgical perspective from the children's cancer group. Pediatr Neurosurg 22:1–7
5. Aydin MV, Sen O, Ozel S, Kayaselcuk F, Caner H, Altinors N (2004) Primary primitive neuroectodermal tumor within the spinal epidural space: report of a case and review of the literature. Neurol Res 26:774–777
6. Deme S, Ang LC, Skaf G, Rowed DW (1997) Primary intramedullary primitive neuroectodermal tumor of the spinal cord: case report and review of the literature. Neurosurgery 41:1417–1420
7. Dorfmuller G, Wurtz FG, Umschaden HW, Kleinert R, Ambros PF (1999) Intraspinal primitive neuroectodermal tumor: report of two cases and review of the literature. Acta Neurochir (Wien) 141:1169–1175
8. Freyer DR, Hutchinson RJ, McKeever PE (1989) Primary primitive neuroectodermal tumor of the spinal cord associated with neural tube defect. Pediatr Neurosci 15:181–187
9. Harimaya K, Oda Y, Matsuda S, Tanaka K, Chuman H, Iwamoto Y (2003) Primitive neuroectodermal tumor and extraskeletal Ewing sarcoma arising primarily around the spinal column: report of four cases and a review of the literature. Spine 28:E408–412

10. Isotalo PA, Agbi C, Davidson B, Girard A, Verma S, Robertson SJ (2000) Primary primitive neuroectodermal tumor of the cauda equina. Hum Pathol 31:999–1001
11. Jaksche H, Wockel W, Wernert N (1988) Primary spinal medulloblastomas? Neurosurg Rev 11:259–265
12. Kepes JJ, Belton K, Roessmann U, Ketcherside WJ (1985) Primitive neuroectodermal tumors of the cauda equina in adults with no detectable primary intracranial neoplasm—three case studies. Clin Neuropathol 4:1–11
13. Liu HM, Yang WC, Garcia RL, Noh JM, Malhotra V, Leeds NE (1987) Intraspinal primitive neuroectodermal tumor arising from the sacral spinal nerve root. J Comput Tomogr 11:350–354
14. Mawrin C, Synowitz HJ, Kirches E, Kutz E, Dietzmann K, Weis S (2002) Primary primitive neuroectodermal tumor of the spinal cord: case report and review of the literature. Clin Neurol Neurosurg 104:36–40
15. McDermott VG, el-Jabbour JN, Sellar RJ, Bell J (1994) Primitive neuroectodermal tumor of the cauda equina. Neuroradiology 36:228–230
16. Sevick RJ, Johns RD, Curry BJ (1987) Primary spinal primitive neuroectodermal tumor with extraneural metastases. AJNR Am J Neuroradiol 8:1151–1152
17. Smith DR, Hardman JM, Earle KM (1969) Metastasizing neuroectodermal tumors of the central nervous system. J Neurosurg 31:50–58
18. Virani MJ, Jain S (2002) Primary intraspinal primitive neuroectodermal tumor (PNET): a rare occurrence. Neurol India 50:75–80
19. Yavuz AA, Yaris N, Yavuz MN, Sari A, Reis AK, Aydin F (2002) Primary intraspinal primitive neuroectodermal tumor: case report of a tumor arising from the sacral spinal nerve root and review of the literature. Am J Clin Oncol 25:135–139
20. Weber DC, Rutz HP, Lomax AJ, Schneider U, Lombriser N, Zenhausern R, Goitein G (2004) First spinal axis segment irradiation with spot-scanning proton beam delivered in the treatment of a lumbar primitive neuroectodermal tumor. Case report and review of the literature. Clin Oncol (R Coll Radiol) 16:326–331
21. Kim YW, Jin BH, Kim TS, Cho YE (2004) Primary intraspinal primitive neuroectodermal tumor at conus medullaris. Yonsei Med J 45:533–538
22. Kosnik EJ, Boesel CP, Bay J, Sayers MP (1978) Primitive neuroectodermal tumors of the central nervous system in children. J Neurosurg 48:741–746
23. Hadfield MG, Quezado MM, Williams RL, Luo VY (2000) Ewing's family of tumors involving structures related to the central nervous system: a review. Pediatr Dev Pathol 3:203–210
24. Biegel JA, Rorke LB, Packer RJ, Sutton LN, Schut L, Bonner K, Emanuel BS (1989) Isochromosome 17q in primitive neuroectodermal tumors of the central nervous system. Genes Chromosomes Cancer 1:139–147
25. Tsokos M (1992) Peripheral primitive neuroectodermal tumors. Diagnosis, classification, and prognosis. Perspect Pediatr Pathol 16:27–98
26. Siebenrock KA, Nascimento AG, Rock MG (1996) Comparison of soft tissue Ewing's sarcoma and peripheral neuroectodermal tumor. Clin Orthop Relat Res 329:288–299
27. Ladanyi M, Lewis R, Garin-Chesa P, Rettig WJ, Huvos AG, Healey JH, Jhanwar SC (1993) EWS rearrangement in Ewing's sarcoma and peripheral neuroectodermal tumor. Molecular detection and correlation with cytogenetic analysis and MIC2 expression. Diagn Mol Pathol 2:141–146
28. Packer RJ, Goldwein J, Nicholson HS, Vezina LG, Allen JC, Ris MD, Muraszko K, Rorke LB, Wara WM, Cohen BH, Boyett JM (1999) Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a children's cancer group study. J Clin Oncol 17:2127–2136
29. Krasin MJ, Rodriguez-Galindo C, Billups CA, Davidoff AM, Neel MD, Merchant TE, Kun LE (2004) Definitive irradiation in multidisciplinary management of localized Ewing sarcoma family of tumors in pediatric patients: outcome and prognostic factors. Int J Radiat Oncol Biol Phys 60:830–838
30. Barker LM, Pendergrass TW, Sanders JE, Hawkins DS (2005) Survival after recurrence of Ewing's sarcoma family of tumors. J Clin Oncol 23:4354–4362