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CASE-BASED UPDATE

Pediatric extraspinal sacrococcygeal ependymoma (ESE): an Italian AIEOP experience of six cases and literature review

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Abstract

Background Primary pediatric extraspinal sacrococcygeal ependymoma (ESE) is a very rare disease, poorly described in literature, whose diagnostic, therapeutic, and follow-up approach is still controversial.

Methods We describe six cases of pediatric ESE treated at Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) centers in Italy since 1983, with a review of the literature.

Results All six patients had primary sacrococcygeal disease (two presacral and four subcutaneous) with median age of 10 years. Three patients were males, and two of them are metastatic at diagnosis; 3/6 had myxopapillary ependymoma grade I and 3/6 had classic ependymoma grade II. Five patients underwent surgical resection with complete removal only in one case with coccygectomy. Adjuvant chemoradiotherapy was administered to one metastatic patient obtaining a complete remission. Two patients relapsed at 3 and 8 years from diagnosis: they were treated with salvage chemotherapy (high-dose sequential chemotherapy with myeloablative regimen in one case), surgery, and radiotherapy achieving complete remission (CR). All six patients are in complete continuous remission (CCR) at a median follow-up of 12.8 years.

Conclusions Pediatric patients with this peculiar disease need to be referred to specialized pediatric cancer centers that can provide multidisciplinary treatment after a centralized pathology review. Our experience highlights the role of chemotherapy and radiotherapy in adjuvant and relapse setting. The final prognosis is relatively optimistic, but with a careful follow-up due to the high risk of recurrence.

Keywords Pediatric ependymoma · Coccygectomy · Radiotherapy · Chemotherapy

Introduction

Ependymoma is the third most common pediatric brain tumor, originating mainly from the walls of the ventricular system; it accounts for only 6% of intracranial gliomas, but for more than 60% of spinal cord tumors [1, 2]. Of all primary brain tumors, ependymomas have the greatest propensity to occur outside the central nervous system (CNS). Extraspinal ependymoma is a very rare entity that may develop at various different sites. It most often originates from the subcutaneous tissue of the sacrococcygeal area with no demonstrable connection to the spinal cord; more rarely, it can originate from the presacral/pelvic region. Very uncommon sites include the mediastinum, lung, and liver [3–5]. Extraspinal sacrococcygeal ependymoma (ESE) is a very rare tumor, accounting for less than 5% of all spinal ependymomas [6]. Some case reports of pediatric ESE in the literature describe primary tumors of the skin and soft tissue in the sacrococcygeal region, with no evidence of any connection to the spinal cord [7, 8].

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Historical background

ESE was first described by Mallory in 1902 [9].

Some studies report a slight male predominance [10], while others describe a balanced gender distribution [11, 12]. Bimodal peaks in the disease's incidence have been suggested for ESE in the sacral region, one peak at less than 8 years of age and one in the fourth decade of life [13]; some authors have reported that ESE occurs more than intraspinal ependymoma in younger patients [8, 14]. Patients' ages at diagnosis range from 3 months to > 80 years, with a mean of 26 years [10, 12, 15]. ESE typically occurs in two characteristic regions: the soft subcutaneous tissue posterior to the sacrum or the presacral space anterior to the sacrum, in the retrorectal recess. Under the age of 18 years, the sacrococcygeal area is the more common primary site; ovarian ESE becomes more frequent beyond the adult age.

The largest pediatric series of pediatric ESE was reported in 2014 [11] with seven cases and a median age of 7.4 years (range 3 weeks–17 years), but without any clinical information related to treatment (Table 1).

Clinical presentation

If the lesion lies posterior to the sacrum, its peculiar presenting symptoms are a slow-growing mass in the intergluteal fold, which is occasionally painful and often misdiagnosed as a pilonidal cyst or other benign tumors. If the origin is pelvic, the ESE is usually larger on discovery, a palpable mass detectable on pelvic or rectal examination associated with bowel and bladder dysfunction and, rarely, signs/symptoms of nerve root involvement such as saddle anesthesia, loss of ankle jerk, or poor rectal sphincter tone [10, 12, 13, 16].

Diagnosis

The histogenesis of these lesions is very controversial, but three different hypotheses are worth exploring; the first is that it might originate from the coccygeal medullary vestige, an ependymal cell-lined cavity that is a remnant of the neural tube, over the tip of the coccyx [16]. This hypothesis would be supported by the observation that most of these types of ESE are of the myxopapillary variant, which is characteristic of an ependymoma arising from the filum terminale [17]. This theory was confirmed by Bale and Maiorana, who found postcoccygeal ependymal rests in embryos and in 10/15 random infant necropsies [18, 19]. Other authors suggest that the tumor develops from a residual, congenitally ectopic ependymal cell originating from the filum terminale. This hypothesis is supported by the correlation with defects in the neural arch (such as spina bifida), found in around 20–30% of patients with ependymoma [20–23]. A third hypothesis is that a germ cell origin with exclusive neuroectodermal differentiation has also been considered, which could explain the disease's ovarian, mesovarian, and mediastinal localizations [22] .

The majority of ESE are myxopapillary grade I WHO like their spinal counterpart [6]. Immunohistochemical reactions usually show positivity for GFAP, EMA, and negativity for Olig2.

Classic ependymoma (grade II WHO) is more frequent in ESE located in the ovary/mediastinum [6]. Unlike CNS ependymomas, adult ESE are often strongly and diffusely positive for estrogen and progesterone, thus providing an opportunity for hormone-based therapies.

Many other diseases need to be ruled out in the differential diagnosis, including pilonidal cyst, benign ependymal rest, teratoma, lipoma, chordoma, myxoid chondrocarcinoma, metastatic mucoid carcinoma, metastatic carcinoid, clear cell carcinoma, neurofibroma, and inflammatory diseases [24–26].

Management

Standard management options for pediatric ESE are not known; it seems that the chances of survival improve with gross total resection to prevent any local relapse. Complete removal is technically feasible for most postsacral tumors, but a combined approach (neurosurgical and pelvic) may be necessary for presacral tumors. Surgical coccygectomy is recommended if the tumor adheres to the bone [17] and repeated excisions for local recurrences achieve good results. Some authors [13, 27] have recommended coccygectomy as part of the primary surgical treatment. Aktuğ et al. [27] conducted a review on 22 pediatric sacrococcygeal ESE reported since 1963, finding that there were no local recurrences in cases whose coccyx had been removed (four patients, with a mean follow-up of 3 years), whereas 5/7 patients who had not undergone coccygectomy experienced a local relapse. Sonneland et al. reported that ESE tend to metastasize more frequently than their intrameningeal spinal counterpart [10]. Metastases to the lung, pleura, bone, lymph nodes, and subcutaneous tissues are attributed to an easier access to vascular and lymphatic vessels [28], and a prolonged and very careful follow-up is consequently recommended. Metastatic spread correlates with the specific extraspinal localization, subcutaneous tumor being at greater risk of metastases than presacral disease, which is more likely to relapse locally [29]. There may be a lengthy interval (even 10–20 years) between the primary lesion's detection and resection, and the development of distant metastases, as in other low-grade malignancies; several reports describe distant metastases being found 10–20 years after a patient's primary diagnosis [12, 16, 17, 28].

Table 1 lists all cases of pediatric ESE reported in the literature since 1963. Cimino [11] described seven pediatric

Table 1 All cases of pediatric ESE reported in literature since 1963

Authors	Presenting age	Sex	Presentation	Histology	Metastases	Treatment	Coccigectomy	Relapse	PFS	Treatment at relapse	Follow-up	Notes
Wolff 1972	4	M	Subcutaneous	Myxopapillary	N	Surgery	NA	- Inguinal node - Lung	30 mos	Surgery	20 YRS NA	Spina bifida occulta
Morantz 1979	7	M	Subcutaneous	Papillary	N	Surgery	No	- Local - Inguinal nodes - Lung and pleural effusion	11 years	Surgery CT RT	15 YRS Died	–
	5	M	Presacral	Anaplastic ependymoma	N	Surgery Radiotherapy Chemotherapy	NA	- Lung	1 year	Biopsy CT RT	18 MOS Died	–
Bale 1980	4	F	Subcutaneous	NA	N	Surgery	NA	No	14 years	NA	14 YRS	Connatal
Helwig and stern 1984	17	F	NA	NA	NA	NA	NA	- Local - Lung - Pleural	6 months	NA	5 YRS	–
Gerston 1985	2	M	Presacral	Myxopapillary	N	Surgery	NA	No	NA	NA	Alive	–
Ciraldo 1986	9 months	F	Subcutaneous	Myxopapillary	N	Surgery	Yes	No	NA	NA	Alive	–
Kramer 1988	15	M	Subcutaneous	NA	N	Surgery	NA	-Local - Inguinal node	9 years	Surgery CT RT	20 YRS	–
Gupta 1992	18 MOS	M	Subcutaneous	Myxopapillary	Inguinal node	Surgery	NA	Locally	1 month	NA	NA	Connatal
Botti 1994	10.5	NA	Subcutaneous	NA	Left buttock	Surgery	NA	No	NA	NA	NA	Connatal
Webber 1997	Newborn	M	Presacral	NA	N	Surgery	NA	Locally	2 months	Surgery coccigectomy	NA	Connatal
Ilhan 1998	8	M	Subcutaneous	Myxopapillary	N	Surgery	Yes	No	20 months	NA	20 months	–
Johnson 1999	7	M	Sacrococcygeal	Grade II	N	Surgery	Yes	No	8 years	NA	8 YRS	–
Aktuğ 2000	5	M	Subcutaneous	Myxopapillary	N	Surgery	Yes	No	3 years	NA	3 YRS	–
Rao 2002	16 months	F	Presacral	Myxopapillary	N	Surgery CT	Yes (histologically negative)	No	NA	NA	Alive	–
Akpolat 2003	7	M	Subcutaneous	Myxopapillary	N	Surgery	NA	No	NA	NA	Alive	–
Tröbs 2006	9	M	Subcutaneous	Myxopapillary	N	Surgery	Yes (histologically negative)	No	NA	NA	NA	–
Beschorner 2007	14 months	M	Subcutaneous	Grade IV myxopapillary and ependymoblastic differentiation	N	Surgery	NA	No	NA	NA	Alive	- Schinzel-Giedion syndrome - Spina bifida occulta
Chakraborti 2012	11 months	F	Sacrococcygeal	Grade IV myxopapillary and anaplastic differentiation	N	Surgery	Yes	Inguinal node	6 months	Surgery CT	Alive	–
Cimino 2014	7 patients Mean 7.4 yrs;3 weeks–17 years range	4F/3M	NA	Myxopapillary	NA	NA	NA	NA	NA	NA	NA	–
Dogan 2016	9	F	Subcutaneous	Myxopapillary	N	Surgery	NA	No	NA	NA	Alive	Connatal

NA, not available; *YRS*, years; *MOS*, months

patients with myxopapillary ESE, none of whom developed metastases or recurrences, whereas 2/4 children with spinal tumors experienced a recurrence after surgery and radiotherapy. In an earlier study on 23 evaluable patients with ESE, Helwig [16] found that 4 (17%) developed metastases; the youngest of these patients, a 17-year-old female, underwent surgical excision of the primary tumor, but developed pleural and lung dissemination 6 months later and died 5 years after her diagnosis. There are another three reports [30–32] of children aged 18 months, 11 months, and 4 years whose ESE metastasized to the inguinal lymph nodes: one of them had a component of anaplastic ependymoma but surgery alone achieved a CCR, and a 4-year-old child experienced a lung relapse 19 years after diagnosis and was treated with surgery, achieving a CR at 1 year. Another report [33] described a 10-year-old child with multifocal localizations (in the pilonidal area and left buttock), who achieved CR after surgical excision alone. Kramer [14] described a 15-year-old male with subcutaneous ESE treated with surgical excision at diagnosis who experienced two local relapses (9 and 19 years after diagnosis), then a third local relapse (20 years later) associated with inguinal metastatic lymph nodes, treated with surgery and focal radiotherapy (50.4 Gy).

The role of radiotherapy in pediatric ESE is not clear. Adjuvant radiotherapy has been recommended after subtotal resections, in the case of inoperable tumor, after the removal of recurrent lesions, or in the event of metastatic dissemination [13, 17], but conclusive data on its real effectiveness are lacking. Some authors recommend a total dose of 50 Gy to the lesion [13, 20] which is unlikely to cause myelopathy. There have been a few cases in which moderate doses of irradiation (30–45 Gy) after incomplete surgery have obtained satisfactory progression-free survival rates and symptom relief [34], while other authors have reported discouraging effects of radiotherapy [14, 35].

The role of chemotherapy is also still unclear. Vaigawala [28] used an aggressive combination of chemotherapeutic agents in a relapsing patient. Yu et al. [36] administered methotrexate and doxorubicin to a relapsing patient with pleural metastases, achieving unsatisfactory results, and Morantz [13] used polychemotherapy for two relapsing pediatric patients, reporting no evidence of relief. On the other hand, Rao [37] used neoadjuvant chemotherapy consisting of 3 cycles of cisplatin/etoposide and bleomycin in a 16-month-old female with a large pelvic mass, achieving a more than 50% reduction in the size of the lesion, plus another three adjuvant courses, achieving a CR. Hwang [38] used topotecan and carboplatin (based on an in vitro chemosensitivity test), inducing a partial response, followed by complete tumor resection and adjuvant doxorubicin/gemcitabine, with no tumor recurrence. Mogler [5] administered imatinib (based on c-kit expression on the tumor tissue) and carboplatin/etoposide chemotherapy for a huge pelvic tumor, obtaining its stabilization.

The use of hormonal suppressive agents has been largely unexplored. There are some reports of hormonal therapy being used for spinal [39–41] and extraaxial ependymomas. Neoadjuvant gonadotropin-releasing hormone treatment in a patient with large ovarian ependymoma (with a positive nuclear reactivity for estrogen, progesterone, and androgen receptors) obtained a reduction in tumor size [42]. A combination of tamoxifen and etoposide for a relapsing spinal myxopapillary ependymoma was able to stabilize the tumor [43]. Therapies inhibiting specific molecular pathways have been sporadically assessed: imatinib for lung metastases of sacrococcygeal ependymoma had no effect, while administering sorafenib for 1 year achieved disease stabilization [44].

Prognosis and outcome

Presacral tumors are more prone to local recurrence [13, 45], with an incidence of recurrence estimated at 60% and a high mortality rate (75%). It is worth noting, however, that these percentages come from reports dating from a time before centralized pathology reviews were in use, and they are consequently likely to be overestimated. In the case of subcutaneous tumors, local recurrences are less frequent (25% at 15 years), but distant metastases are more common [46].

Exemplary case description

Here, we describe six cases of pediatric ESE treated in Italy since 1983 collected by reviewing the medical records of patients referred to our department or at AIEOP Italian centers. Histologic diagnosis were reviewed by retrieving the blocks and centralizing them at the Italian Pathology reference center. Parents signed an informed consent. Immunohistochemistry for GFAP, EMA (dot-like), and Olig2, proliferation index evaluated with Ki-67, and hormonal expression of androgens or estrogen/progesterone receptors were evaluated.

The patients' clinical characteristics are shown in Table 2.

Three of the six patients were male, and the patients' median age at diagnosis was 10 years (range 4–16 years). All six patients had primary sacrococcygeal disease (two in the presacral region and four in the subcutaneous tissue). Two had metastases at the time of their diagnosis, which involved the inguinal lymph nodes, acetabulum, ischium, and sacral vertebrae in one case and the parauterine region in the other. A growing palpable painless intergluteal lesion was the presenting symptom in five patients, while enuresis and sacral pain were reported only for one metastatic patient with presacral tumor. The coccyx was infiltrated in two cases, but coccygectomy was only performed in one; five patients underwent primary surgery, achieving complete removal in only one. Of the two patients with metastases on presentation, one initially underwent biopsy for diagnostic

Table 2 Patients' characteristics

Patients	Sex	Age at diagnosis	Histology grade WHO	Site of disease	Coccyx infiltration	Metastases at diagnosis	First-line therapy	Site of relapse	Treatment at relapse	Follow-up (OS, years)
1	M	14	II	Presacral	Yes	No	Surgery (marginal)	na	na	Alive (6)
2	F	8	II	Presacral	Yes	Yes (inguinal lymph nodes, acetabulum ischium and sacral vertebrae)	- Diagnostic biopsy - Chemotherapy - Radiotherapy - surgery	na	na	Alive (26)
3	F	4	I	Subcutaneous	No	Yes (parauterine lymph nodes)	Surgery (complete with coccygectomy)	- Neoplastic iliac thrombosis - Lung - Broad ligament - Retroperitoneal/ mediastinal adenopathies	- High-dose CT - Myeloablative melphalan - Pelvic radiotherapy	Alive (15)
4	M	12	II	Subcutaneous	No	No	Surgery (marginal)	na	na	Alive (6)
5	M	16	I	Subcutaneous	No	No	surgery (marginal)	na	na	Alive (11)
6	F	7	I	Subcutaneous	Not known	No	Surgery (marginal)	Inguinal adenopathies	- Lymphadenectomy - Chemotherapy	alive (33)

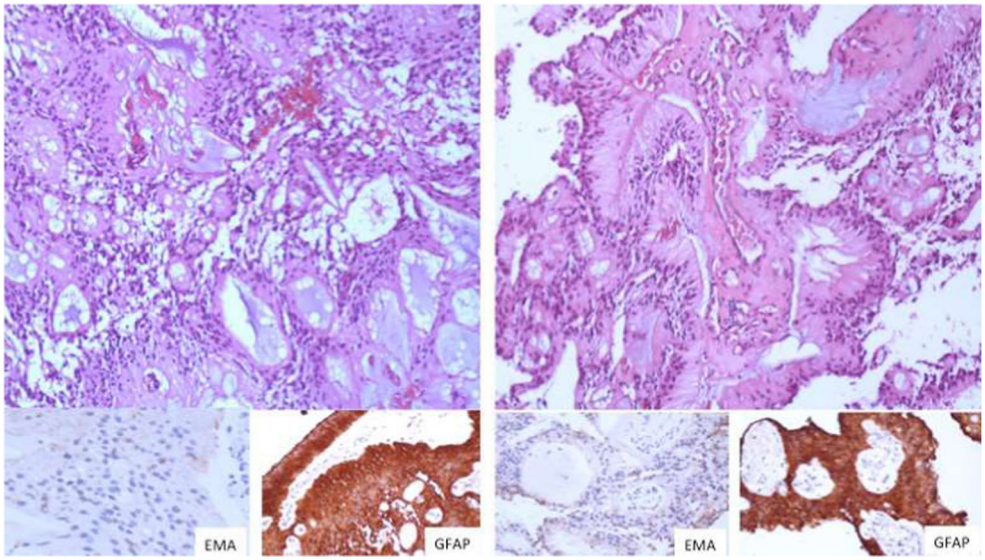

Fig. 1 Tumors are characterized by cuboidal and elongated tumor cells arranged in a papillary fashion around vascularized stromal cores. Neoplastic cells are GFAP positive and show dot-like EMA positivity

purposes, followed by wide tumor resection at the end of the treatment, and the other had extensive, complete surgical resection of the primary site at diagnosis. A centralized pathology review was feasible in four out of six cases and confirmed an original diagnosis of grade I myxopapillary ependymoma in two cases and grade II classic ependymoma in two patients, originally diagnosed as neuroepithelial tumor and malignant myoepithelioma respectively. Myxopapillary ependymoma showed tumor cells arranged around vessels with mucoid degeneration. Classic ependymomas were characterized by columnar tumor cells arranged around infrequent central lumen and perivascular pseudorosettes.

Immunohistochemistry showed positivity for GFAP and EMA (dot-like) and negativity for Olig2 (Fig. 1). Proliferation index evaluated with Ki-67 ranged from 2 to 20%; in detail, it was equal to 25 and 20% in the metastatic patient at relapse and at diagnosis respectively. It could be hypothesized that there is a correlation between metastatic disease and high level of Ki-67, but the number of patient is too low; therefore, a confirmation and a larger study are needed. Estrogen and progesterone antigens were expressed in one case.

Adjuvant therapy was only administered to one metastatic patient, with standard-dose chemotherapy (vincristine, carboplatin, epirubicin, actinomycin-D, ifosfamide, etoposide), which achieved a partial response, followed by radiotherapy (40.4 Gy) to the pelvis, including the acetabulum, ischium, and sacral vertebrae; the patient subsequently underwent wide resection of the residual lesion. Two of the six patients experienced a recurrence (3 and 8 years after their primary diagnosis):

– One (patient 6) had subcutaneous disease at diagnosis treated with incomplete surgery, subsequently developed an inguinal lymph node metastasis, and was treated with inguinal lymphadenectomy and salvage chemotherapy (alternating 3 cycles of cisplatin 30 mg/m^2 and etoposide 150 mg/m^2 on days 1–3 with 3 cycles of doxorubicin 20 mg/m^2 on days 1–3, vincristine 1.5 mg/m^2 and cyclophosphamide 330 mg/m^2 on days 1, 8, and 15).

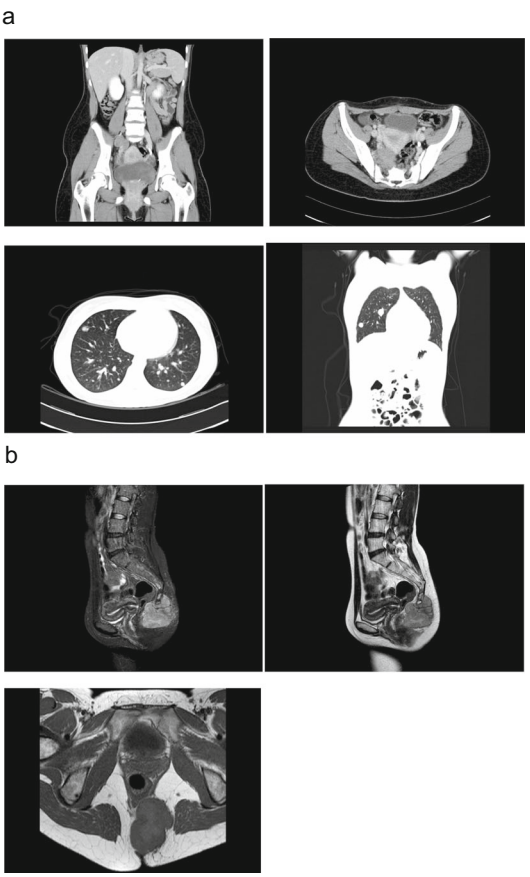

Fig. 2 **a** Patient 3: computed Tomography imaging at relapse: right hypodense hemipelvic lesion with iliac adenopathies. Multiple bilateral parenchymal lung nodules. **b** MRI of subcutaneous intergluteal localization at diagnosis

Table 3 Patient 3: strategy of treatment, sequential (*VAdmIfo*, vincristine 2 mg/m^2/day 1, Adriamycin 45 mg/m^2/day 1–2, ifosfamide 3000 mg/m^2/day 1–3; *CEto* cyclophosphamide 4000 mg/m^2/day 1, etoposide 200 mg/m^2/day 1–3; *VAdmC*, vincristine 2 mg/m^2/day 1, Adriamycin 40 mg/m^2/day 1–2, cyclophosphamide 1200 mg/m^2/day1; *EtoIfo* etoposide 100 mg/m^2/day 1–3, ifosfamide 1800 mg/m^2/day 1–5)

1	Vincristine 2 mg/m^2 Adriamycin 45 mg/m^2/day for 2 days Ifosfamide 3000 mg/m^2/day for 3 days	
2	Cyclophosphamide 4000 mg/m^2 Etoposide 200 mg/m^2/day for 3 days	Mobilization with G-CSF 10 μg/kg and autologous stem cell harvest
3	VAdmIfo	
4	CEto	
5	Vincristine 2 mg/m^2 Adriamycin 40 mg/m^2/day for 2 days Cyclophosphamide 1200 mg/m^2	
6	Etoposide 100 mg/m^2/day for 3 days Ifosfamide 1800 mg/m^2/day for 5 days	
7	VAdmC	
8	Eto Ifo	
9	High-dose melphalan 140 mg/m^2	
10	Radiotherapy	50.4 Gy (fraction/day = 1.8 Gy) on pelvic region Boost 3.6 Gy (in 2 fractions) on sacral region

– The other (patient 3) had metastatic parauterine lesion at diagnosis and experienced a local recurrence with neoplastic iliac thrombosis, lung and broad ligament metastases, and retroperitoneal and mediastinal adenopathies (Fig. 2); she received high-dose sequential chemotherapy (see Table 3) with a partial response of the pelvic lesions and pulmonary/mediastinal metastases, followed by myeloablative melphalan with peripheral autologous stem cell transplantation, then pelvic radiotherapy (54 Gy). Both of these relapsing patients achieved CR. All six patients are alive in CCR with a median follow-up of 12.8 years. The two girls given pelvic radiotherapy are currently being treated with estrogen-progestin replacement therapy for iatrogenic amenorrhea.

Conclusion

While adult data suggest a very marginal role for chemotherapy, more favorable results have been reported in the pediatric context. The numbers involved in pediatric series are too small for any definitive conclusions to be drawn on this issue; however, our experience, albeit on a very small series, points to a role for chemotherapy, in both the neo/adjuvant setting and at relapse, since a partial remission was achieved with sequential high-dose chemotherapy before radiotherapy. Although the final prognosis for pediatric ESE is relatively optimistic, patients need to be followed up carefully for many years due to the risk of recurrence.

Moreover, it is crucial that patients with rare oncological pediatric diseases such as ESE are referred to specialized pediatric cancer centers that can provide for a centralized reliable diagnosis as well as the surgical and complementary treatments warranted in an updated multidisciplinary view.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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