Case Reports in Women's Health 38 (2023) e00523

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

An unusual presentation of extraskeletal vaginal Ewing sarcoma: A case report

Sarah Addison [a], Rebecca Ganzon [b], Han Gil Kim [b], Hans Iwenofu [c], Gabriel Tinoco [b,*]

[a] The Ohio State University College of Medicine, Columbus, OH, USA
[b] Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA
[c] Department of Radiology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

ARTICLE INFO

Keywords:
Case report
Vaginal Ewing sarcoma
Sarcoma

ABSTRACT

Ewing sarcoma (ES) is a rare, aggressive malignancy that typically arises from bone and is seen more in adolescents and young adults. In contrast, extraskeletal Ewing sarcoma (EES) is more prevalent in adults and women [1,2]. There is no standard treatment for extraskeletal tumors, especially those in sensitive areas, such as the vagina, where resection may cause a large cosmetic or functional deformity. This case features a woman in her 20s who presented with painless vaginal bleeding and was found to have a 4 × 5 × 4-mm EES of the posterior vaginal wall. The presentation raised both reproductive and functional concerns, as the patient was young, sexually active and of childbearing age. The patient underwent treatment with radiation therapy and chemotherapy every 3 weeks. Given the lack of guidance and proclivity of EES to metastasize, it is paramount to proceed with standard-of-care treatment even if it is small and there is a lack of metastatic disease. For women with vaginal EES who are of childbearing age, brachytherapy rather than surgical resection may be a more favorable option when considering the location and the potential impact of vaginectomy.

1. Introduction

Ewing sarcomas (ES) are aggressive malignancies, predominately found in children and adolescents, with a higher incidence in males. These are relatively uncommon tumors, with an incidence of 2.93 per 1 million individuals in the US [1,2]. The majority of ES are primary tumors of the bone; however, 20% to 30% manifest as primary extraskeletal or soft-tissue tumors [2]. EES is more likely to affect adults and is more common in women [2]. Extraskeletal, or soft-tissue, involvement can occur in any part of the body but is more frequently observed in the lower extremities [3]. ES tends to metastasize to the lungs, skeletal system, and bone marrow, leading to poor outcomes [4]. In recent years, due to treatment innovations in chemotherapy and surgery, the overall survival rate for localized ES has increased to above 70%; however, 25% of these patients will experience disease recurrence after initial treatment [1,2].

Although encouraging, the majority of these advances in treatment have focused on children and adolescents with primary bone tumors. There is far less information on the best course of treatment for those with EES, especially adult patients, who generally have a worse prognosis [5].

Here, one such case is presented: a young woman with a primary ES of the vagina. Thus far, there are only 17 case reports of this diagnosis, which are briefly summarized in Table 1.

2. Case Presentation

A woman in her 20s—gravida 5, parity 5—with no significant past medical history, presented to an emergency department with heavy vaginal bleeding after palpating a painless mass in her vagina.

2.1. Clinical Findings

At the time of initial presentation, the patient declined a pelvic exam, but an ultrasound scan revealed a 4 × 5 × 4-mm cystic lesion along the vaginal wall. A pelvic exam with her gynecologist revealed a posterior vaginal mass that bled but was not tender at palpation. Pathological review of an excisional biopsy demonstrated a 2.0 × 1.8 × 0.6-cm mass containing a fusion between the EWSR1 exon 7 and FLI exon 6 genes, consistent with the diagnosis of ES. Selected histopathologic images with associated descriptions are shown in Fig. 1.

* Corresponding author.
E-mail address: Tinoco@osumc.edu (G. Tinoco).

https://doi.org/10.1016/j.crwh.2023.e00523
Received 14 June 2023; Received in revised form 22 June 2023; Accepted 23 June 2023
Available online 25 June 2023

Table 1
Case reports of vaginal Ewing sarcoma.

Author	*Location*	*Treatment*	*Prognosis*	*Metastatic?*
Rekhi 2019 [6]	Cervicovaginal	Chemotherapy	Unknown/ Lost to follow-up	Unknown
Rekhi 2019 [6]	Anterior vaginal wall	Chemotherapy (VDC/IE) & external beam radiation	Disease free at 18 months post-treatment	No
Cross 2017 [7]	Vaginal, posterior to bladder	Chemotherapy	Metastatic spread to lung and brain; on palliative treatment	Yes
Cross 2017 [7]	Posterior vaginal	Chemotherapy and surgical resection	Disease free at 12 months post-treatment	No
Modi 2016 [8]	Lateral wall of the vagina	Chemotherapy and external beam radiation	Disease free at treatment conclusion	No
Pang 2012 [9]	Anterior and posterior vaginal	External beam radiation plus brachytherapy	Death 18 months post-treatment completion due to disease progression	Yes
Bancalari 2012 [10]	Retrocervical posterior vaginal wall	Chemotherapy and surgical resection	Disease free at 20 months post-diagnosis	No
Machado 2013 [11]	Upper third of the anterior vaginal wall	Chemotherapy	Death 22 months after diagnosis due to disease progression	Yes
Rekhi 2010 [12]	Anterior and posterior vaginal walls and anterior sacrum	Chemotherapy (VDC/IE)	Disease free at completion of induction phase	No
Yip 2009 [13]	Vaginal introitus	External beam radiation, subsequent Surgical resection of metastasis	Disease free at 18 months post-resection.	Yes
Al-Tamimi 2009 [14]	Posterior wall of the lower third of the vagina	Surgical resection, followed by adjuvant chemotherapy, external beam radiation and brachytherapy)	Unknown	No
McCluggage 2007 [15]	Case series – including one case involving anterior vaginal wall	Unknown	Unknown	Unknown
Liao 2004 [16]	Lower third of the posterior vaginal wall	Surgical resection, adjuvant chemotherapy, and adjuvant external beam radiation plus brachytherapy	Disease free at 36 months post-resection.	No
Gaona-Luviano 2003 [17]	Distal third of the vagina	Surgical resection, chemotherapy. External beam radiation and brachytherapy	Disease free at 20 months post-resection	No
Petković 2002 [18]	Rectovaginal septum	Chemotherapy, external beam radiation and brachytherapy	Unknown	No
Farley 2000 [19]	Distal third of the vagina	Chemotherapy, external beam radiation, and brachytherapy	Disease free at 48 months post-treatment	No
Vang 2000 [20]	Vaginal lesion, not otherwise specified	Surgical resection and chemotherapy	Disease free at 19 months post-diagnosis	No

2.2. Diagnostic Assessment

Soon thereafter, she presented to another institution, where she had an MRI scan of the pelvis with and without contrast and a chest CT scan with contrast. She displayed no evidence of gross residual or metastatic disease. A PET scan did not reveal hypermetabolic lesions; however, it revealed nonspecific increased uptake within the uterus and ovaries, which is not abnormal for a patient in her late 20s. The scan also revealed nonspecific reactive uptake in the tonsils and nasopharynx.

Initial pathology results showed small round neoplastic cells indicating several possible diagnoses, including EES, desmoplastic small round cell tumors, primitive neuro-ectodermal tumors, small-cell carcinoma, rhabdomyosarcoma, HPV-associated carcinoma including neuroendocrine carcinoma, neuroblastoma, lymphoma, melanoma, and Merkel cell carcinoma. The tumor had CD99 positivity and a lack of staining for HPV association (p16 and HPV-ISH). Pathognomonic findings of the excisional biopsy confirmed the diagnosis of EES: fusion of the EWSR1 exon 7 and FLI exon 6 genes.

2.3. Therapeutic Intervention

Fertility-preservation strategies were discussed prior to starting systemic therapies; however, the patient declined. The patient received standard-of-care ES/EES treatment with vincristine, doxorubicin, cyclophosphamide/ifosfamide and etoposide (VDC/IE). She could not tolerate the dose-dense schedule (every two weeks) due to myelosuppression. Thus, she was switched to a standard schedule of every three weeks. After extensive discussion with a multidisciplinary sarcoma team, brachytherapy was determined to be the most appropriate treatment for the primary site. This decision was made primarily by considering the side-effects of the alternatives: surgery and stereotactic radiation. She tolerated the brachytherapy well. Currently, the patient is completing her adjuvant chemotherapy portion, aiming for a 14-cycle goal, per the National Comprehensive Cancer Network (NCCN) guidelines.

2.4. Follow-Up and Outcomes

To date (Fig. 2), the patient has completed four cycles of neoadjuvant chemotherapy with VDC/IE followed by brachytherapy (4000 cGy in 8 fractions to the vaginal cuff). Although the optimal consolidation treatment for this patient has not been standardized, brachytherapy was offered to preserve organ function and fertility.

Post-brachytherapy, she resumed adjuvant chemotherapy and has completed 4 adjuvant doses thus far. She is planned to complete 14 total

cycles of chemotherapy per NCCN guidelines. Secondary to treatment, she has suffered neutropenic fever, acidosis, anemia requiring transfusion, and anxiety but currently has no radiographic evidence of disease progression or recurrence.

3. Discussion

This presentation is such a rarity that no standard of practice exists for treating vaginal ES. The traditional presentation of EES is treated with neoadjuvant chemotherapy followed by surgical resection and additional adjuvant chemotherapy. Radiation therapy is also occasionally used. However, a combination of chemotherapy and radiation therapy may be the best option for this patient due to the sensitive location of the tumor. A surgical excision would likely result in a full vaginectomy, which could pose significant emotional distress at the patient's age.

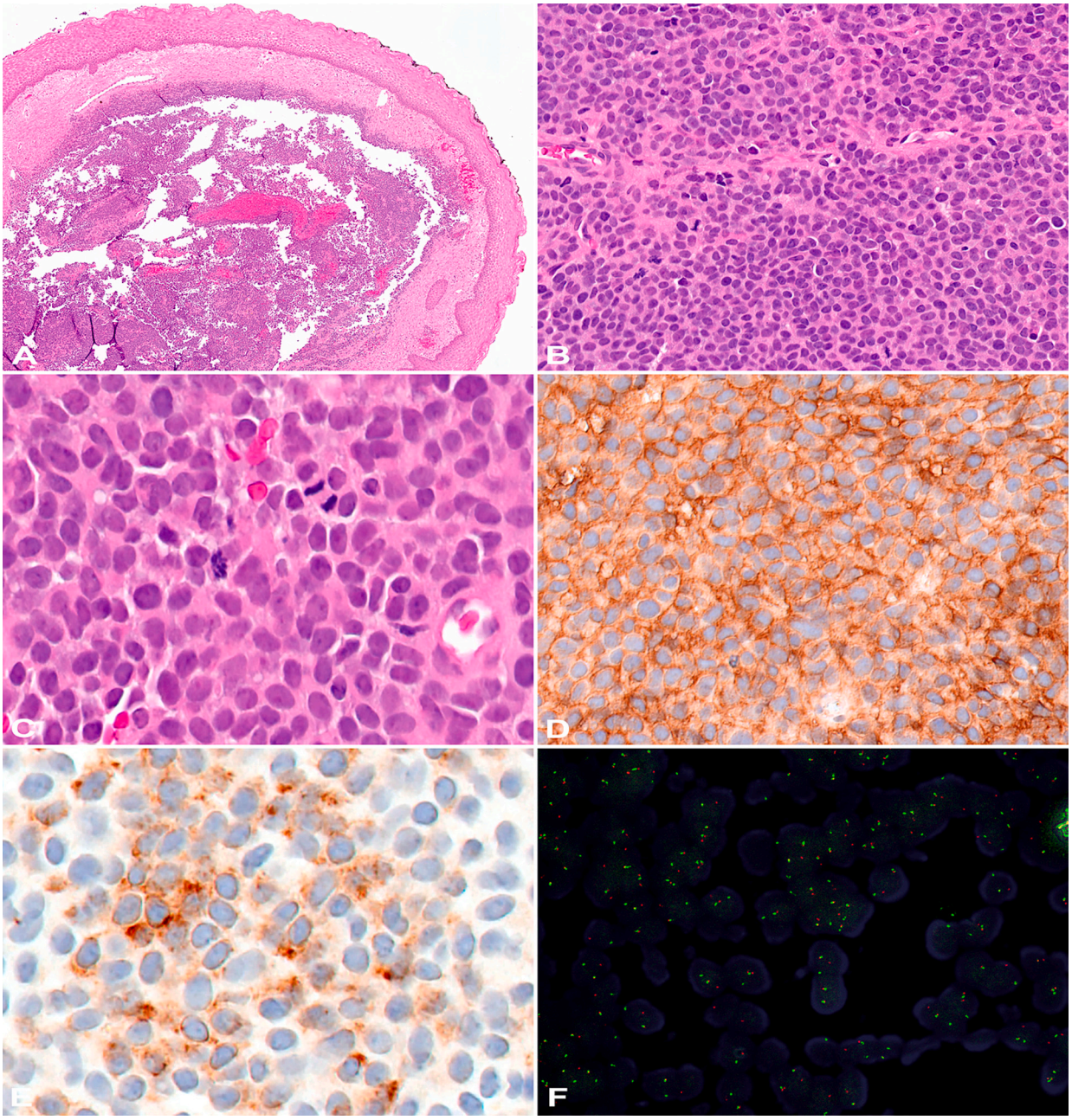

Fig. 1. Select histopathologic slides.
Legend:
A (Hematoxylin and Eosin; Mag × 100): Infiltrative tumefactive mass underlying the squamous mucosal lining of the vagina.
B (Hematoxylin and Eosin; Mag × 200): tumor is composed of diffuse uniform sheets of malignant small round blue cells.
C (Hematoxylin and Eosin; Mag × 400): The malignant cells show uniforms round to oval blue cells with high nuclear-cytoplastic ration, scant cytoplasm, and fine powdery chromatin. Mitotic figures are easily discernible in this field.
D (CD99 Immunohistochemical stain; Mag × 400): The tumor cells show strong and diffuse CD99 immunoreactivity with characteristic membranous pattern.
E (Synaptophysin immunohistochemical stain; Mag × 400): The tumor cells show focal reactivity for synaptophysin.
F: Fluorescence in situ hybridization (Mag × 200), showing positive rearrangement of the EWSR1 gene. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

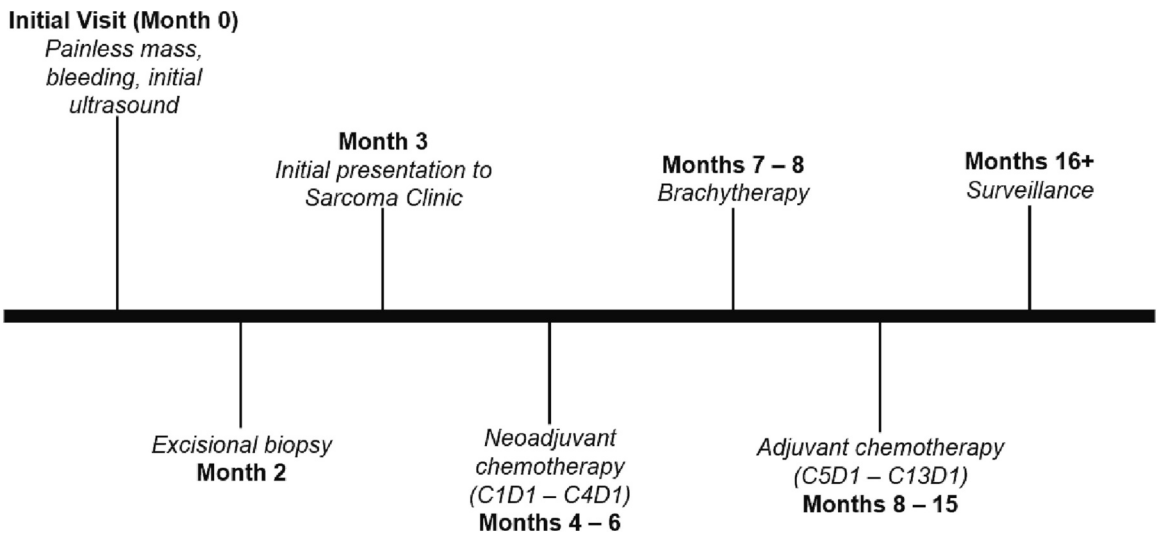

Fig. 2. Timeline.

There is some precedent for opting for chemotherapy rather than surgical resection. Of the other 16 documented cases of primary Ewing sarcoma of the vagina available, seven noted treatment of the tumor with surgical resection, eight noted chemotherapy alone, and the last one was treated with radiotherapy only. Notably, a 2009 case report by Yip and colleagues noted that their patient's vaginal tumor was not resected due to the location and young age of the patient [13]. However, in a 2017 case highlighted by Cross and colleagues, the authors were able to surgically resect the tumor while keeping the architecture of the vagina intact [7]. This demonstrates that removing the tumor with adequate negative margins may be feasible while maintaining the integrity of the vagina.

Over the past years, there has been debate over the optimal systemic therapies for the treatment of localized ES; however, very recently, a phase III, open-label study (EE2012) conducted in Europe confirmed VDC/IE superiority, consolidating its role as the current standard first-line treatment for all patients with ES [21]. Future treatment options may include the use of CRISPR-Cas9 technology, and further research is underway [22]. Given the lack of guidance and proclivity of EES to metastasize, it is paramount to proceed with standard-of-care treatment even when it is small and there is a lack of metastatic disease. For women with vaginal EES who are of childbearing age, brachytherapy rather than surgical resection may be a more favorable option when considering the location and the potential impact of vaginectomy.

Contributors

Sarah Addison contributed to interpreting and validating the data, drafting the original manuscript, and reviewing and editing the manuscript.

Rebecca Ganzon contributed to patient care, interpreting the data, and reviewing and editing the manuscript.

Han Gil Kim contributed to acquiring data and reviewing and editing the manuscript.

Hans Iwenofu contributed to acquiring data, visualization, and reviewing and editing the manuscript.

Gabriel Tinoco contributed to patient care, conception of the case report, acquiring, interpreting, and validating the data, visualization, drafting the original manuscript, reviewing and editing the manuscript, and project administration.

All authors approved the final submitted manuscript.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patient consent

The patient provided written consent to the publication of the case report and accompanying images.

Provenance and peer review

This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

References

[1] S. Jiang, G. Wang, J. Chen, Y. Dong, Comparison of clinical features and outcomes in patients with extraskeletal vs skeletal Ewing sarcoma: an SEER database analysis of 3,178 cases, Cancer Manag. Res. 10 (2018) 6227–6236.
[2] R.G. Maki, Pediatric sarcomas occurring in adults, J. Surg. Oncol. 97 (4) (2008) 360–368.
[3] G. Galyfos, G.A. Karantzikos, N. Kavouras, A. Sianou, K. Palogos, K. Filis, Extraosseous Ewing sarcoma: diagnosis, prognosis and optimal management, Indian J. Surg. 78 (1) (2016) 49–53.
[4] G.G. Meshram, N. Kaur, K.S. Hura, Ewing's sarcoma with distant metastasis: a brief note on management and emerging therapies, Clin. Pract. 9 (3) (2019) 1111.
[5] K.N. Ganjoo, S. Patel, The treatment outcome for adult patients with Ewing's sarcoma, Curr. Oncol. Rep. 15 (4) (2013) 372–377.
[6] B. Rekhi, R. Agrawal, O. Shetty, K.K. Deodhar, S. Menon, J. Ghosh, R. Kerkar, A. Maheshwari, Five rare cases of Ewing sarcoma, including with epithelial differentiation, involving the female genital tract, displaying EWSR1 rearrangement: diagnostic challenge and treatment implications, Ann. Diagn. Pathol. 41 (2019) 1–7.
[7] N.M. Cross, A.L. Stanescu, E.R. Rudzinski, D.S. Hawkins, M.T. Parisi, Vaginal Ewing sarcoma: an uncommon clinical entity in pediatric patients, J. Clin. Imaging Sci. (2017) 17.
[8] G. Modi, I. Madabhavi, A. Patel, A. Anand, H. Panchal, S. Parikh, K. Baldaniya, S. Revannasiddaiah, Primary vaginal Ewing's sarcoma: a rare case report, J. Obstet. Gynaecol. India 66 (Suppl. 2) (2016) 690–693.
[9] X. Pang, P. Chen, F. Wen, Y. Zhang, Primary Ewing's sarcoma/primitive neuroectodermal tumor of the vagina in a 54-year-old woman: a case report, Arch. Gynecol. Obstet. 285 (4) (2012) 1031–1033.
[10] E. Bancalari, E. de Álava, J.C. Tardío, Primary vaginal Ewing sarcoma: case report and review of the literature, Int. J. Surg. Pathol. 20 (3) (2012) 305–310.
[11] L. Machado, A. Al-Hamdani, D.K. Sankhla, M.S. Al-Moundhri, Extraosseous Ewing sarcoma of the vagina: a rare entity, Ann. Saudi Med. 33 (2) (2013) 182–186.

[12] B. Rekhi, S. Qureshi, R. Basak, S.B. Desai, S. Medhi, P. Kurkure, S. Menon, A. Maheshwari, N.A. Jambhekar, Primary vaginal Ewing's sarcoma or primitive neuroectodermal tumor in a 17-year-old woman: a case report, J. Med. Case Rep. 4 (2010) 88.
[13] C.M. Yip, S.S. Hsu, N.J. Chang, J.S. Wang, W.C. Liao, J.Y. Chen, S.H. Liu, C. H. Chen, Primary vaginal extraosseous Ewing sarcoma/primitive neuroectodermal tumor with cranial metastasis, J. Chin. Med. Assoc. 72 (6) (2009) 332–335.
[14] H. Al-Tamimi, A.A. Al-Hadi, A.H. Al-Khater, I. Al-Bozom, N. Al-Sayed, Extraskeletal neuroectodermal tumour of the vagina: a single case report and review, Arch. Gynecol. Obstet. 280 (3) (2009) 465–468.
[15] W.G. McCluggage, V.P. Sumathi, M.R. Nucci, M. Hirsch, P. Dal Cin, M. Wells, A. M. Flanagan, C. Fisher, Ewing family of tumours involving the vulva and vagina: report of a series of four cases, J. Clin. Pathol. 60 (6) (2007) 674–680.
[16] X. Liao, X. Xin, X. Lü, Primary Ewing's sarcoma-primitive neuroectodermal tumor of the vagina, Gynecol. Oncol. 92 (2) (2004) 684–688.
[17] P. Gaona-Luviano, E. Unda-Franco, L. González-Jara, P. Romero, H. Medina-Franco, Primitive neuroectodermal tumor of the vagina, Gynecol. Oncol. 91 (2) (2003) 456–458.
[18] M. Petković, G. Zamolo, D. Muhvić, M. Coklo, S. Stifter, R. Antulov, The first report of extraosseous Ewing's sarcoma in the rectovaginal septum, Tumori 88 (4) (2002) 345–346.
[19] J. Farley, J.D. O'Boyle, J. Heaton, S. Remmenga, Extraosseous Ewing sarcoma of the vagina, Obstet. Gynecol. 96 (5 Pt 2) (2000) 832–834.
[20] R. Vang, J.K. Taubenberger, C.M. Mannion, K. Bijwaard, A. Malpica, N.G. Ordonez, F.A. Tavassoli, S.A. Silver, Primary vulvar and vaginal extraosseous Ewing's sarcoma/peripheral neuroectodermal tumor: diagnostic confirmation with CD99 immunostaining and reverse transcriptase-polymerase chain reaction, Int. J. Gynecol. Pathol. 19 (2) (2000) 103–109.
[21] B. Brennan, L. Kirton, P. Marec-Berard, N. Gaspar, V. Laurence, J. Martin-Broto, A. Sastre, H. Gelderblom, C. Owens, N. Fenwick, S. Strauss, V. Moroz, J. Whelan, K. Wheatley, Comparison of two chemotherapy regimens in patients with newly diagnosed Ewing sarcoma (EE2012): an open-label, randomised, phase 3 trial, Lancet 400 (10362) (2022) 1513–1521.
[22] S.T. Cervera, C. Rodriguez-Martin, E. Fernandez-Tabanera, R.M. Melero-Fernandez de Mera, M. Morin, S. Fernandez-Penalver, M. Iranzo-Martinez, J. Amhih-Cardenas, L. Garcia-Garcia, L. Gonzalez-Gonzalez, M.A. Moreno-Pelayo, J. Alonso, Therapeutic potential of EWSR1-FLI1 inactivation by CRISPR/Cas9 in Ewing sarcoma, Cancers (Basel) 13 (15) (2021).