Pathology - Research and Practice 215 (2019) 387–391

Contents lists available at ScienceDirect

Pathology - Research and Practice

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

Case report

Colonic Ewing Sarcoma/PNET associated with liver metastases: A systematic review and case report

Pietro Parcesepe[a,*,1], Guido Giordano[b,**,1], Caterina Zanella[c], Jacopo Giuliani[d], Filippo Greco[d], Andrea Bonetti[d], Massimo Pancione[e], Erminia Manfrin[a], Enrico Molinari[f], Tiziana Pia Latiano[b], Mario Rosario D'Andrea[g], Matteo Fassan[h], Nunzio Olivieri[i], Andrea Remo[j]

[a] Department of Diagnostics and Public Health – Section of Pathology, University and Hospital Trust of Verona, Verona 37134, Italy
[b] Fondazione IRCCS Casa Sollievo della Sofferenza, UO di Oncologia Medica, 71013 San Giovanni Rotondo, Foggia, Italy
[c] Pathology Unit, ULSS9 "Scaligera", 37122 Verona, Italy
[d] Oncology Unit, ULSS9 "Scaligera", 37122 Verona, Italy
[e] Department of Sciences and Technologies, University of Sannio, 82100 Benevento, Italy
[f] Surgery Unit, ULSS9 "Scaligera", 37122 Verona, Italy
[g] Medical Oncology Unit, San Filippo Neri Hospital – ASL Roma 1, 00135, Roma, Italy
[h] Department of Medicine (DIMED), University of Padua, 35121, Padova, Italy
[i] Department of Biology, University of Naples, Federico II, 80134 Napoli, Italy
[j] Mater Salutis" Hospital, ULSS9, 37045 Legnago, Verona, Italy

ARTICLE INFO

Keywords:
Ewing Sarcoma
Colon
Rectum
PNET
Liver metastases
Extra osseous sarcoma

ABSTRACT

Ewing Sarcoma is a highly lethal undifferentiated tumor of bone. ES is a small round cell tumor with etiological and characteristic chromosomal translocations between TET/FET (TLS/FUS, EWSR1, and TAF15) and ETS (E26 transformation-specific) family genes. Generally, therapeutic approach for metastatic Ewing Sarcoma includes both local (surgery and radiotherapy) and systemic (chemotherapy) disease control with an overall cure rate of 20%. For extra-osseous tumors, the most common primary sites of disease are trunk, extremities, head and neck, retroperitoneum. Among other sites, Ewing Sarcoma/PNET may also rarely arise in colon and rectum. Even if colonic Ewing Sarcoma/PNET have been previously reported in 5 cases, none of those reports came from right side of the colon. In this article, we report the first case of right-sided Ewing Sarcoma with synchronous liver metastases completely responding to first line chemotherapy. Furthermore, we provide a systematic qualitative review of the current literature on adult colorectal Ewing Sarcoma using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

1. Introduction

Ewing Sarcoma (ES), was described by James Ewing in 1921 as an highly lethal undifferentiated tumor of bone [1]. Actually, ES family includes Ewing Sarcoma, neuroectodermal tumors (PNET), and small-cell thoracopulmonary neoplasm (Askin tumors). This group comprise tumors that show varying degrees of neural differentiation but common cytogenetic and molecular features. The majority of ES are diagnosed in the second decade of life, while 20–30% are in the first decade. Occurrences are rare in individuals over 30 years and under the age of 5 years [2]. ES is a round small cell tumor with etiological and characteristic chromosomal translocations between TET/FET (TLS/FUS,

* Corresponding author at: Fondazione IRCCS Casa Sollievo della Sofferenza, UO di Oncologia Medica, Viale Cappuccini 1, 71013 San Giovanni Rotondo, Foggia, Italy.
** Corresponding author at: Department of Diagnostics and Public Health – Section of Pathology, University and Hospital Trust of Verona, P.le L.A. Scuro, 37134 Verona, Italy.
E-mail addresses: parcesepe.pietro@gmail.com (P. Parcesepe), giordano.guido81@gmail.com (G. Giordano), caterina.zanella@aulss9.veneto.it (C. Zanella), jacopo.giuliani@aulss9.veneto.it (J. Giuliani), filippo.greco@aulss9.veneto.it (F. Greco), andrea.bonetti@aulss9.veneto.it (A. Bonetti), massimo.pancione@unisannio.it (M. Pancione), erminia.manfrin@univr.it (E. Manfrin), enrico.molinari@aulss9.veneto.it (E. Molinari), latiano.tiziana@gmail.com (T.P. Latiano), mariorosario.dandrea@aslroma1.it (M.R. D'Andrea), matteo.fassan@unipd.it (M. Fassan), n.olivieri@studenti.unina.it (N. Olivieri), remino76@yahoo.it (A. Remo).
[1] Equal contributors.

https://doi.org/10.1016/j.prp.2018.11.021
Received 7 October 2018; Received in revised form 25 November 2018; Accepted 27 November 2018

EWSR1, and TAF15) and ETS (E26 transformation-specific) family genes [3,4]. Generally, ES primary site is bone, but it can also occur in other tissues including pancreas, liver, adrenal gland, esophagus, and uterus [5]. ES/PNET is extremely rare in colon and rectum and although it has been previously reported in this location in only 5 cases [6–10], none of them came from right side of the colon. In this article, we report the first case of right-sided ES with synchronous liver metastases completely responding to first line chemotherapy. Furthermore, we provide a systematic qualitative review of the current literature on adult colorectal ES using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2. Methods

Patient's medical history including comorbidities, concomitant medications, ES diagnosis and treatment were taken from clinical records. Written informed consent for the case publication was obtained from the patient. The Ethics Committee approved all procedures. A systematic review of the literature was performed in compliance with the PRISMA guidelines. Screening was performed by reviewing article titles or full text up to February 2018 using electronic the database MEDLINE. The primary search terms included "Ewing Sarcoma", "colon" and "rectum" in the article titles. The extracted citations were then screened for duplicates. Later operator "and" was applied on the extracted records by use of the abovementioned terms to narrow the scope of the review. Sixty articles met eligibility criteria for our qualitative systematic review, 2 were excluded as duplicates and 47 because not relevant. Finally, 11 papers were included in the qualitative analysis (Fig. 1) [11].

3. Case report

On April 2016 a 31 years old men presented to Legnago's Hospital "Mater Salutis" for pre-syncopal episode. The patient referred neither cancer familiar history nor comorbidities. He only suffered for fatigue during last 2 months. The clinical evaluation evidenced pale skin and mucosae with heart rate of 110 bpm and blood pressure 110/70 mmHg. Electrocardiography and neurological examination showed no cardiac abnormalities or central nervous system disease. Blood test were within normal range except for anemia (Haemoglobin = 8.0 g/dl, Mean Corpuscolar Volume = 72 fl, Hematocrit = 27.1%). Patient had no acute bleeding episodes. The following colonoscopy showed a large, ulcerative lesion in the right colon that was easily bleeding in contact with the endoscope. Biopsy of the lesion was performed and histological examination showed morphological features of undifferentiated tumor. (immunohistochemistry: CD45, 20, 3, 5, 117 negative, MNF116 negative, synaptophysin negative, CD99 positive, Ki67 10%). Contrast Enhanced Computed Tomography (CT Scan) confirmed the right sided colon lesion and evidenced liver metastasis (1.1 x 1.3 cm) in the IIIrd segment (Fig. 2). Tumor markers were performed and both CEA and CA19.9 were within normal values. After multidisciplinary evaluation a video laparoscopic right emicolectomy plus lymphoadenectomy associated with hepatic nodule resection were performed. Grossly, 4 cm (longitudinal) x 3 cm (transversal) tumor, involving the serous superficial face (pT4) was found. Histologically, the neoplasm consisted of small, round blue cells with a solid pattern associated with pseudo-

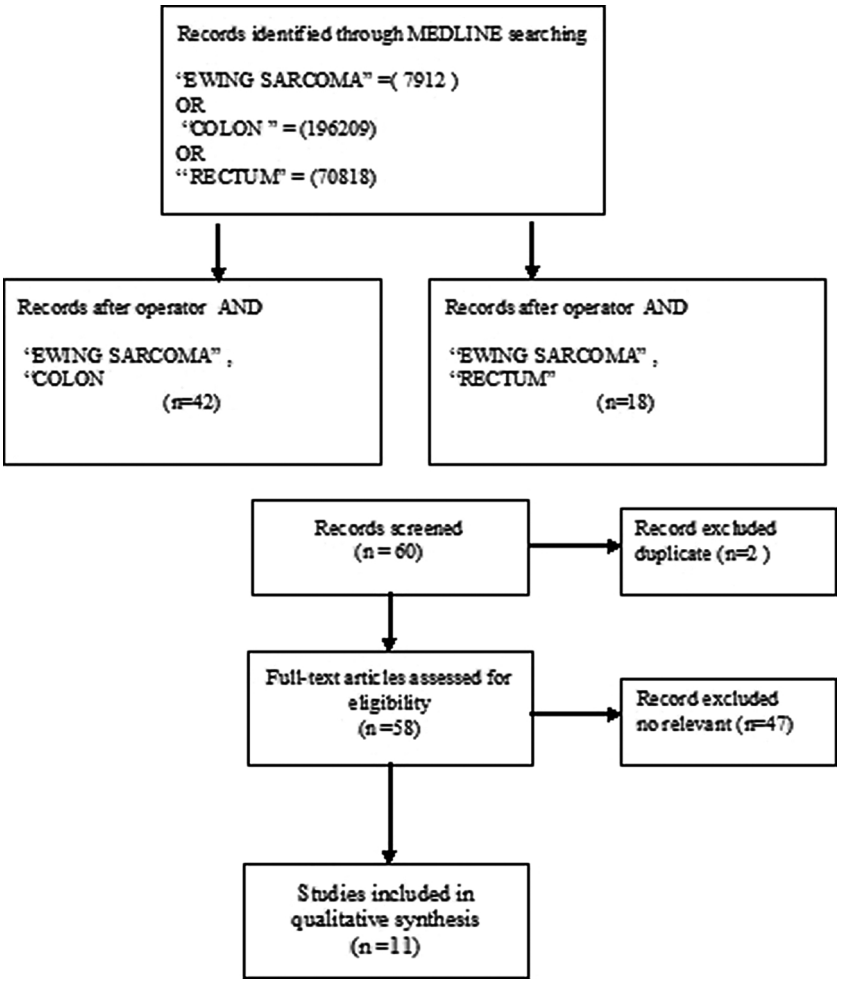

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol used for the systematic review.

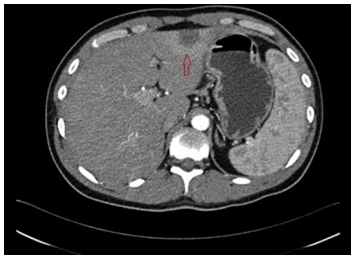

Fig. 2. Baseline CT Scan evidencing single liver metastasis in the IIIrd segment (red arrow) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

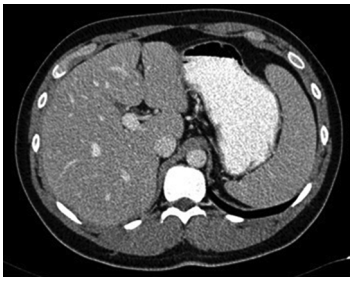

Fig. 4. CT Scan after 3 cycles of chemotherapy evidencing complete response on liver metastasis.

rosettes. Mitoses were 2–3 × 10 HPF. Tumor cells showed positive immunoreactivity for Vimentin and CD99. Results were negative for anti-myogenin, CD34, CD45LC, CDX-2, Cytocheratin 20, Desmin, EMA, Chromogranin A, HMB 45, Melan-A, Myeloperoxidase, MNF116, Synaptofisin, TTF1, and WT-1 (Fig. 3). The morphological and immunohistochemical characteristics were suggestive for Ewing Sarcoma/PNET. No one of the 24 resected lymph nodes was involved by carcinoma. The diagnosis was similar for the hepatic nodule. FISH analysis indicated the presence of EWSR1 gene rearrangement and confirmed the ES diagnosis. After surgical treatment, a restaging of the disease was needed in order to decide the following program. PET/CT scan revealed 3 new liver metastases with maximum diameter of 2 cm: 2 lesions in the left lobe and one between VII° e VIII° segment (Standard Uptake Value 7, 5.5 and 6.7, respectively). In June 2016, a first line chemotherapy was started using the VAC regimen (vincristine 2 mg/m^2 i.v., doxorubicin 75 mg/m^2 i.v., cyclophosphamide 1200 mg/m^2 i.v.) day 1 every 21 days, alternating with IE schedule (ifosfamide 1800 mg/m^2 i.v. + mesna i.v. + etoposide 100 mg/m^2 e.v.) day1 -5 every 21 days. Patient's Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 0. After the first cycle, grade 3 febrile neutropenia occurred. Therefore, the patient was recovered in the Oncology Division and he received daily granulocyte colony stimulating growth factors (GC-CSF) and antibiotics with quick normalization of the clinical conditions and blood test. Treatment was continued with same schedule by reducing the dose of 25% without haematological toxicities. Only grade 2 nausea and grade 1 vomiting were observed. Response evaluation with total body CT scan was performed after 3 cycles of chemotherapy evidencing a complete response on the liver metastases (Fig. 4). No other metastatic sites were showed and patient's ECOG PS was 0. Chemotherapy was continued up to six cycles and the final PET/CT scan confirmed a metabolic and radiological complete response in March 2017. Three-monthly clinical and instrumental follow up program was started with no evidence of disease progression up to February 2018.

4. Discussion

ES/PNET is a rare tumor. The incidence for all ages is one case per 1 million people in the Western Countries. The median age of patients

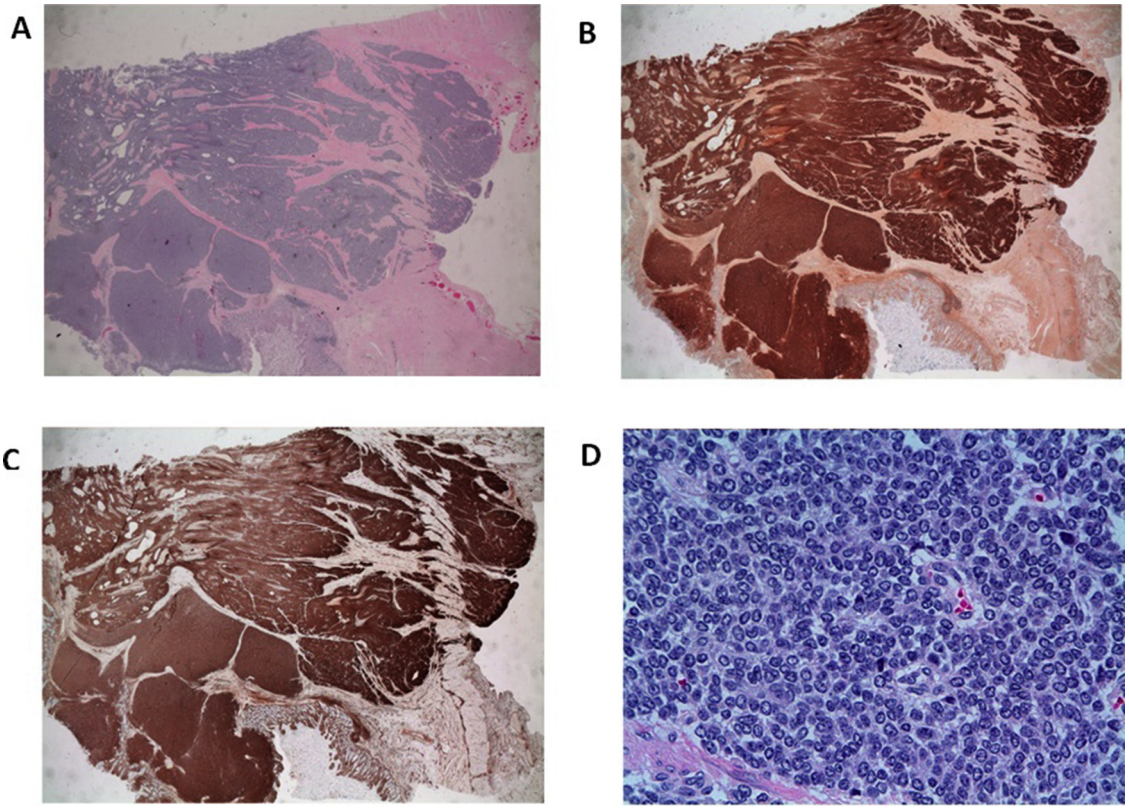

Fig. 3. The tumour showed solid pattern with occasionally dilatated spaces (A; 20x). The immunoistochemistry revelead a strong expression for CD99 (B; 20X) and vimentin (C; 20X) in the small round neoplastic cells (D; 200X).

Table 1
Summary of colorectal ES /PNET cases reported in literature.

	Tumor site	Age	Metastasis at diagnosis	Treatment	Relapse	Treatment	Survival
Kuwabara et al [6]	Descending	59	peritoneum	surgery	retroperitoneum	Surgery	7 m˙ OS[α]
Tokudome et al [7]	Transverse	24	No	surgery	No	No	20 m DFS[+]
Drutt et al [8]	Rectum	17	No	surgery-cht[*,a]	No	No	12 m DFS
	Rectum	34	Liver	surgery + cht[b] + stem cells + cht[c]	No	no	84 m PFS[°]
Vardy et al [10]	Rectum	53	No	surgery + rt + + cht[d]	Lung-brain	cht[1]	24 m OS
Parcesepe et al	ascending	31	liver	surgery + cht[e]	no	no	20 m PFS

[*] cht = chemotherapy.
[a] not reported.
[b] IVAD (ifosfamide 5000 mg/m2 intravenous over 3 days, vincristine 2 mg intravenous day 1, and doxorubicin 20 mg/m2 intravenous days 1–3, with mesna support, granisetron and dexamethasone) for five cycles every 3 weeks.
[c] stem cells + cht (peripheral blood stem cell supported high-dose chemotherapy with carboplatin at a dose calculated to give an area under the curve (AUC) of 15 intravenous, etoposide 100 mg/m2 intravenous twice daily ×4 and melphalan 140 mg/m2 intravenous).
[d] 25 fractions of radiotherapy to the pelvis and four cycles of adjuvant chemotherapy with cyclophosphamide, vincristine, and doxorubicin.
[e] VAC (vincristine 2 mg/m2 i.v., doxorubicin 75 mg/m2 i.v., cyclophosphamide 1200 mg/m2 i.v.) day1 every 21days, alternating with IE (ifosfamide 1800 mg/mq i.v. + mesna i.v. + etoposide 100 mg/mq e.v.) day1 -5 every 21 days.
[+] DFS = Disease Free Survival.
[°] PFS = Progression Free Survival.
[˙] m = months.
[α] OS = Overall Survival.

with ES is 15 years, and more than 50% of patients are adolescents [12]. Generally, ES primary site is bone with a major incidence in lower extremities (41%), pelvis (26%), and chest wall (16%) [13]. For extra-osseous tumors, the most common primary sites of disease are trunk (32%), extremities (26%), head and neck (18%), retroperitoneum (16%) and other sites (9%) [14]. In a pooled analysis of two pediatric clinical trials, patients with extra-skeletal primary tumors were more likely to have an axial primary site, less likely to have large primary tumors and had a statistically significant better prognosis than patients with skeletal primary tumors [15]. Infants and younger patients have a better prognosis than patients aged 15 years and older [16]. Metastatic disease from the beginning has a worse prognosis than non-metastatic disease. Among metastatic sites, lung and bone are the most common localizations and pulmonary disease has a better outcome than other sites [17]. The case reported in this article represents the sixth adult colorectal ES/PNET published so far. In particular, it's the first located in the right colon (Table1). Colorectal ES seems to occur in older patients. In fact the median age according to the current literature is 32,5 years (range 17–59) (Table1). Notably, older age appears as an adverse prognostic factor for all the localizations of ES. Interestingly, the cases reported of colonic ES/PNET show worse prognosis in patients older than 50 years (Table 1). The clinical presentation of the disease in our case, the diagnostic procedures and the following surgical approach were typical of a classic colon cancer. In fact, the previous history of fatigue related to anemia hid an underlying bleeding in the right side of the colon. At the time of disease staging, CT scan detected a single liver lesion. Therefore, surgical resection of the primary, bleeding, symptomatic, colon tumor and liver lesion was performed. Surprisingly, the morphological and immunohistochemistry analyses with positive immune-reactivity for Vimentin, CD99 and moderate staining for KI67 and S100 were suggestive for an undifferentiated neoplasm of the "blue cell tumor" type, and in particular for an ES/PNET. Then FISH analysis indicated the presence of EWSR1 gene rearrangement and confirmed the diagnosis. The corresponding chromosomal translocation is identified in about 85% of patients. In 5–10% of cases EWS is fused with other members of the ETS gene family [18]. As reported in the current literature, 25% of cases have distant metastases at the time of diagnosis. The median time from first symptom to diagnosis of ES is often long, with a median interval reported from 2 to 5 months. Longer times are associated with older age and pelvic primary sites but not related with metastasis, surgical outcome, or survival [19,20]. Current therapeutic options for metastatic ES/PNET include: surgery, radiotherapy and chemotherapy. Standard chemotherapy for patients with metastatic ES is based on the alternating administration of VAC and IE regimens every 21 days. Combining chemotherapy with adequate local-control applied to both primary and metastatic sites often results in complete or partial responses; however, the overall cure rate is 20% [21–23]. The rarity of colorectal ES/PNET does not allow to standardize the optimal therapeutic approach. Therefore, algorithm should be decided case by case according the stage of the disease, patients' condition, disease localization and treatment aims. In our case the primary tumor bleeding, led the patient to anemia and pre-syncopal episode, and surgery was needed. Liver metastasectomy was also indicated because the lesion was single and technically resectable. Unfortunately, the post-surgical restaging showed three liver metastases detected by PET/CT scan. Despite the quick relapse after surgery, the patient showed a complete response to standard first line chemotherapy, even complicated by febrile neutropenia. Chemotherapy for ES treatment is very intensive and highly toxic. Adverse events should be early detected and appropriately managed in order to avoid treatment discontinuations. Literature for colonic ES is poor but the previously reported cases show that chemotherapy, when combined with local disease control may have a very positive impact on patients' survival.

5. Conclusion

Colonic ES/PNET is a very rare neoplasm that should be carefully identified and diagnosed in order to choose the best therapeutic approach. Therefore, a multidisciplinary evaluation is highly recommended since the beginning to maximize patients benefit and outcomes. The case described in this article represents the first report of right sided colonic ES. The surgical management both of the primary tumor and the synchronous liver metastasis and the following first line chemotherapy led to a complete and durable response. However further investigation on larger series of visceral ES/PNET should be required in order to better understand the molecular pathway and identify potential therapeutic targets.

Consent for publication

The patient provided written informed consent for publication of any associated data and accompanying images

Competing interests

The authors declare that they have no competing interests.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' contributions

GG, NO and PP performed the literature research, wrote the paper and assessed figure and tables. AR and JG collected the case. Er. M reviewed and confirmed the histological diagnosis. CZ, MP, GC, AB, FG, En. M, MRDA, and TPL made the revision. AR, PP and GG supervised the project.

Ethics approval

The Ethics Committee Lazio 1 n. 2001/2017 approved all procedures

Availability of data and materials

The data that support the findings of this study are available from the corresponding author on reasonable request

References

[1] J. Ewing, Diffuse endothelioma of bone, Proc. New York Path Soc. 21 (1921) 17–24.
[2] M. Bernstein, H. Kovar, M. Paulussen, R.L. Randall, A. Schuck, L.A. Teot, Ewing's sarcoma family of tumors: current management, Oncologist 11 (5) (2006) 503–519.
[3] E.D. Alava, S.L. Lessnick, P. Sorensen, WHO Classfication of Tumours of Soft Tissue and Bone, International Agency for Research on Cancer (IARC), Lyon, France, 2013.
[4] L.P. Dehner, Primitive neuroectodermal tumor and Ewing's sarcoma, Am. J. Surg. Pathol. 17 (1) (1993) 1–13.
[5] Primary Ewing's sarcoma/primitive neuroectodermal tumor of the ileum: case report of a 16-year-old Chinese female and literature review, Diagn. Pathol. 12 (2017) 37.
[6] K. Kuwabara, H. Ishida, K. Shirakawa, M. Yokoyama, H. Nakada, Y. Hayashi, et al., Primitive neuroectodermal tumor arising in the colon: report of a case, Surg. Today 36 (2) (2006) 193–197.
[7] N. Tokudome, K. Tanaka, M.H. Kai, K. Sueyoshi, S. Matsukita, T. Setoguchi, Primitive neuroectodermal tumor of the transverse colonic mesentery defined by the presence of EWS-FLI1 chimeric mRNA in a Japanese woman, J. Gastroenterol. 37 (7) (2002) 543–549.
[8] R. Drut, M. Drut, C. Muller, A. Marron, Rectal primitive neuroectodermal tumor, Pediatr. Pathol. Mol. Med. 22 (5) (2003) 391–398.
[9] O.M. Aboumarzouk, et al., PNET/Ewing's sarcoma of the rectum: a case report and review of the literature, BMJ Case Rep. (2009).
[10] J. Vardy, A.M. Joshua, S.J. Clarke, P.M. Yarrow, B.P. Lin, Small blue cell tumors of the rectum. Case 1. Ewing's sarcoma of the rectum, J. Clin. Oncol. 23 (4) (2005) 910–912.
[11] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, The PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009) e100097.
[12] M.U. Jawad, M.C. Cheung, E.S. Min, et al., Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: an analysis of 1631 cases from the SEER database, 1973-2005, Cancer 115 (15) (2009) 3526–3536.
[13] R.B. Raney, L. Asmar, W.A. Newton Jret al., Ewing's sarcoma of soft tissues in childhood: a report from the Intergroup Rhabdomyosarcoma Study, 1972 to 1991, J. Clin. Oncol. 15 (2) (1997) 574–582.
[14] R.G. Rowe, D.G. Thomas, S.M. Schuetze, et al., Ewing sarcoma of the kidney: case series and literature review of an often overlooked entity in the diagnosis of primary renal tumors, Urology 81 (2) (2013) 347–353.
[15] T. Cash, E. McIlvaine, M.D. Krailo, et al., Comparison of clinical features and outcomes in patients with extraskeletal versus skeletal localized Ewing sarcoma: a report from the Children's Oncology Group, Pediatr. Blood Cancer 63 (10) (2016) 1771–1779.
[16] H. van den Berg, U. Dirksen, A. Ranft, et al., Ewing tumors in infants, Pediatr. Blood Cancer 50 (4) (2008) 761–764.
[17] M. Paulussen, S. Ahrens, A.W. Craft, et al., Ewing's tumors with primary lung metastases: survival analysis of 114 (European Intergroup) Cooperative Ewing's Sarcoma Studies patients, J. Clin. Oncol. 16 (9) (1998) 3044–3052.
[18] O. Delattre, J. Zucman, T. Melot, et al., The Ewing family of tumors–a subgroup of small-round-cell tumors defined by specific chimeric transcripts, N. Engl. J. Med. 331 (August (5)) (1994) 294–299.
[19] N. Esiashvili, M. Goodman, R.B. Marcus Jr, Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: surveillance epidemiology and end results data, J. Pediatr. Hematol. Oncol. 30 (6) (2008) 425–430.
[20] J.F. Brasme, M. Chalumeau, O. Oberlin, et al., Time to diagnosis of Ewing tumors in children and adolescents is not associated with metastasis or survival: a prospective multicenter study of 436 patients, J. Clin. Oncol. 32 (18) (2014) 1935–1940.
[21] L.M. Barker, T.W. Pendergrass, J.E. Sanders, et al., Survival after recurrence of Ewing's sarcoma family of tumors, J. Clin. Oncol. 23 (19) (2005) 4354–4362.
[22] S. Ferrari, R. Luksch, K.S. Hall, et al., Post-relapse survival in patients with Ewing sarcoma, Pediatr. Blood Cancer 62 (6) (2015) 994–999.
[23] A. McTiernan, D. Driver, M.P. Michelagnoli, et al., High dose chemotherapy with bone marrow or peripheral stem cell rescue is an effective treatment option for patients with relapsed or progressive Ewing's sarcoma family of tumours, Ann. Oncol. 17 (8) (2006) 1301–1305.