Indian J Surg (February 2016) 78(1):49–53
DOI 10.1007/s12262-015-1399-0

REVIEW ARTICLE

Extraosseous Ewing Sarcoma: Diagnosis, Prognosis and Optimal Management

George Galyfos[1,4] · Georgios A. Karantzikos[1] · Nikolaos Kavouras[1] · Argiri Sianou[2] · Konstantinos Palogos[1] · Konstantinos Filis[3]

Received: 28 November 2014 / Accepted: 3 November 2015 / Published online: 13 November 2015

Abstract Extraosseous Ewing sarcomas (EESs) are rare tumours originating from soft tissues. Their clinical picture depends mainly on the primary site of the sarcoma. Patient characteristics and outcomes seem to be different in EES compared to patients with skeletal Ewing sarcoma, with implications for patient care and prognosis. However, multimodality therapeutic strategies are recommended for all types of the Ewing tumour family. The available diagnostic tools include ultrasonographic evaluation and computed tomography (CT) or magnetic resonance imaging as well as histopathologic and immunohistochemical tissue examination. Several histologic and genetic biomarkers have been established, although their utilization needs to be further tested by larger prospective studies. Regarding localized disease, the recommended treatment remains surgery. However, chemotherapy can be added to achieve improved survival, with neoadjuvant regimens showing more promising results than adjuvant regimens. Radiotherapy is an option to obtain local control, although its complications have reduced its utilization. In metastatic or recurrent disease, systematic chemotherapy improves survival.

✉ George Galyfos
georgegalyfos@hotmail.com

[1] Department of General Surgery, General Hospital of Chalkis, Chalkis, Greece

[2] Department of Microbiology, Areteion University Hospital, Athens, Greece

[3] 1st Department of Propaedeutic Surgery, University of Athens Medical School, Hippocration Hospital, Athens, Greece

[4] 6 Melinas Merkouri Street, Neon Iraklion, 14122 Athens, Greece

Keywords Extraosseous Ewing sarcoma · Soft tissue sarcoma · Biomarkers · Diagnosis · Therapy

Introduction

Ewing sarcoma (ES) is a poorly differentiated, highly malignant, round cell tumour without cellular or structural differentiation [1]. It shows an aggressive clinical behaviour with high rate of local recurrence and distant metastasis. ES is the second most common malignant bone tumour in children and young adults, although, rarely, it may be of extraskeletal origin [1]. Patients with extraosseous Ewing sarcoma (EES) are of higher mean age and are less likely to be male or White compared to patients with skeletal tumours [2]. Commonly affected extraskeletal sites include the paravertebral spaces, lower extremities, head and neck and pelvis [3]. Other rare locations of EES include the retroperitoneum, omentum, orbit, skin and chest wall [4]. Extraskeletal tumours are more likely to arise from axial locations and less likely to arise from the pelvis [4]. A secondary osseous involvement is rare, even when the mass is located near a bone segment. It can lead to cortical erosion and/or a periosteal reaction [3, 4].

Traditionally, many different modalities and therapeutic methods have been proposed for the treatment of EES. Given that mainly case reports or case series have been published on the subject lately, this review aims to synthesize and present all recent data regarding the diagnosis, treatment and prognosis of this rare entity and attempts to make useful conclusions regarding its proper management.

Diagnosis

EES has no specific clinical manifestation. The most frequently presenting symptom is a rapidly growing mass with local pain [5]. However, the type of accompanying symptoms depends largely on the sarcoma's site of origin. The imaging characteristics of soft tissue ES are non-specific as well. It often presents as a well-limited mass which should not be confused with a benign lesion [6]. Ultrasonography often reveals a heterogeneous mass of low echogenicity with intratumour flow signals in a Doppler study [7]. Computed tomography (CT) shows a large, sharply delineated mass which is relatively of lower or equal density compared to the adjacent muscle [8]. Moreover, post-contrast medium enhancement is intense and heterogenous, with hypodense foci often resulting from intratumour necrosis [8, 9]. On magnetic resonance imaging (MRI), EES is often of low to intermediate signal intensity on T1-weighted images and of high signal intensity on T2-weighted images and exhibits heterogeneous contrast enhancement [10]. MRI is able to provide evidence of non-involvement of the marrow cavity. Radiological differential diagnosis includes rhabdomyosarcoma, malignant fibrous histiocytoma and liposarcoma as well [7].

Definitive diagnosis is made by CT-guided core-needle biopsy or pathological examination of the resected specimen during procedure. EES is confirmed by characteristic features on histologic analysis, histochemistry, immunohistochemistry and electron microscopy [11, 12]. Differential diagnosis includes other small, blue round cell tumours (SBRCTs) and other members of the Ewing family of tumours [13]. Ewing sarcoma/primitive neuroectodermal tumour (EWS/PNET) and other tumours with ES gene rearrangements encompass a malignant and intermediate neoplasm with a broad anatomic distribution and a wide age range but a predilection for soft tissue in children, adolescents and young adults. The overlapping histologic, immunohistochemical, cytogenetic and molecular genetic features create diagnostic challenges despite significant clinical and prognostic differences.

The family of SRBCTs includes malignancies with common morphological and immunohistochemical characteristics [14]. Generally, the term, 'SRBCT' has been reserved for the neoplasms which are located in the skeletal system or in the somatic soft tissue and it is usually not applied to other malignant neoplasms of infants and children that can also be composed predominantly or entirely of small cells, such as Wilms' tumour, hepatoblastoma or medulloblastoma. Traditionally, the main members of the SRCT group have been malignant lymphoma, Ewing's sarcoma, rhabdomyosarcoma and adrenal neuroblastoma. Therefore, immunohistochemistry is one of the most prevalent and convenient methods for pathological diagnosis; however, differentiation between SRBCT subtypes in the absence of valid diagnostic markers is still very challenging. Diagnosis is also complicated in cases with atypical morphology, aberrant immunoprofiles and unusual clinical presentations. A subset of tumours resembling microscopically the ES family, being composed of primitive small round cells and occurring in paediatric or young adult age groups, remain unclassified, being negative for EWSR1, SS18 (SYT), DDIT3 (CHOP) and FOXO1 (FKHR) gene rearrangements by fluorescence in situ hybridization (FISH)/RT-polymerase chain reaction (PCR). A small number of cases sharing the undifferentiated EFT appearance have been characterized recently carrying BCOR-CCNB3 or CIC-DUX4 fusions [15].

Biomarkers

ES/PNET is positive for CD99 (a 32-kDa cell surface glycoprotein encoded by the MIC2 gene); however, expression of CD99 is, by no means, specific for ES/PNET among round cell tumours [11–13, 16]. Although FLI-1 is a variable histochemical marker for ES/PNET, it is also positive in lymphoblastic lymphoma. In contrast, Wilms' tumour gene (WT1) is a positive marker of Wilms' tumour and desmoplastic round cell tumours, whereas it is a negative marker for ES/PNET, neuroblastoma and rhabdomyosarcoma. Electron microscopic features include a specific high nucleus to cytoplasm ratio and aggregated glycogen granules in the cytoplasm [11]. Neural differentiation appears on some cells with polar processes, which may contain microtubules or neurosecretory glands.

Molecular genetic studies by RT-PCR or FISH detect chromosomal translocations, such as t(11;22)(q24;q12), which is positive in 88–95 % of ES/PNET cases [16, 17]. Over 90 % of ES/PNETs feature an 11;22 translocation leading to an EWSR1-FLI1 fusion [18]. EWSR1 has been involved in several translocations and is identified in several other distinct clinicopathological entities: ES/PNETs, desmoplastic small round cell tumour (DSRCT), clear cell sarcoma of soft tissue (ST-CCS), angiomatoid fibrous histiocytoma (AFH), extraskeletal myxoid chondrosarcoma (EMCS) and a subset of myxoid liposarcoma (MLPS) [19]. However, other transcripts have also been reported. Less commonly, a member of the ETS transcription factor family other than FLI-1 is fused with EWSR1. Additionally, recent data support a pivotal role for gene BMI-1 in Ewing sarcoma family tumour (ESFT) pathogenesis [20].

Furthermore, the detection of occult tumour cells in bone marrow and/or peripheral blood samples has been shown to have a predictive value for recurrent disease in patients with non-metastatic Ewing tumours [21]. However, this prognostic factor has not been evaluated in extraskeletal ESs. Finally, independent studies of both small and large tumour cohorts have identified individual and global patterns of copy number alterations as prognostic biomarkers in ES [22]. However, as underlined by Shukla et al. recently, the prognostic role of all the aforementioned biomarkers has been evaluated in

numerous retrospective studies, and therefore, larger prospectively planned cohorts of equivalently treated patients need to further evaluate their significance [23].

Treatment

The National Comprehensive Cancer Network (NCCN) has generated guidelines for the treatment of bone cancers including ESs, and the authors suggest that any member of the Ewing tumour family can be treated according to the same algorithm [24]. The treatment recommended is local treatment (surgery and/or radiotherapy) plus chemotherapy. However, Rud et al. [25] and Covelli et al. [26] have suggested that surgery may have a more important role in EES than in skeletal ES and that complete resection predicts a favourable survival. In another recent study, Qureshi et al. investigated the impact of negative but close resection margins on local recurrence in children with EES [27]. The authors concluded that quantitative extent of negative margins does not influence local control, while achieving a three-dimensional tumour-free margin should be the goal of surgical resection [27]. Therefore, the golden standard of treatment for localized disease remains surgery, although there is a worse disease-free survival in sarcoma patients without margin-negative surgery [28, 29].

EES is quite radiosensitive, but improvements in surgical technique and the risks associated with radiation (secondary malignancies) have reduced the reliance upon radiation [30]. Some researchers have underlined the important role of preoperative radiotherapy (RT) for successful local treatment in spinal Ewing tumours [31]. Definitive RT is indicated when only an intralesional resection is possible [32]. Debulking procedures do not improve local control and are associated with additional unnecessary morbidity. In the experience of the European Cooperative Ewing Sarcoma Studies (CESS) and EICESS trials, patients who had an intralesional resection followed by RT had the same local control rate as patients who had RT alone [33]. Therefore, RT could be indicated to avoid intralesional resections. Moreover, after a poor histologic response and wide resection, postoperative RT may improve local control [33]. Additionally, Iwata et al. concluded that carbon ion RT for unresectable EES may show favourable local control with unsatisfactory results for distant control [34]. However, more data are needed from randomizing studies designed to evaluate the role of RT in the treatment of EES.

Regarding the use of chemotherapy, it plays a pivotal role in the treatment of ESs. Recent studies have shown that neoadjuvant and adjuvant chemotherapies produce comparable results in patients with localized disease [35]. Chemotherapy can be provided after surgery to improve overall survival rates and reduce the likelihood of tumour recurrence [36]. In the large randomized Intergroup Rhabdomyosarcoma Studies (IRS) studies, where patients with EES consisted almost 5 % of nearly 3000 recruited patients, the addition of doxorubicin in patients of localized, gross residual EES did not achieve an overall survival benefit [37]. However, there are no studies comparing chemotherapy alone versus surgery for EES as far as prognosis is concerned. Neoadjuvant chemotherapy and delayed resection increase the likelihood of complete tumour resection with a negative microscopic margin and avoid external beam radiation in chest wall ES/PNET [38]. Moreover, Krasin et al. concluded that local disease control and overall outcome for patients with ESFT managed by multiagent chemotherapy before surgery was excellent, with local disease control rates remaining near 90 % at 10-year follow-up [39]. However, data show that patients with extraosseous primary sites of disease may fare less well with the latter approach [40].

A combination of several agents is used to obtain a higher response rate. First-generation regimens consisted of the combination of vincristine, cyclophosphamide, actinomycin D and doxorubicin (VAcCD). Second-generation regimens incorporated ifosfamide and later etoposide with improved disease-free survival for patients with localized disease [41]. Recent data indicate that there is no significant difference between anthracycline and platinum-based chemotherapies regarding event-free survival and overall survival [42]. However, Castex et al. conclude that patients with EES should be treated with osseous ES regimens, probably due to the anthracycline use [36]. Currently, chemotherapy with alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide (VDC/IE) cycles and primary tumour treatment with surgery and/or radiation therapy constitute the usual approach to localized ES in North America [43].

The current generation of clinical trials has attempted to improve survival by maximizing the chemotherapy dose per cycle, increasing the total number of cycles provided or decreasing the interval between cycles ('dose-dense' therapies) [44, 45]. A recent randomized trial by Womer et al. concluded that interval-compressed chemotherapy with VDC/IE and filgrastim is more effective in localized ES than the same chemotherapy given at standard 3-week intervals, with no increase in toxicity [43]. Given that the aforementioned data are the result of randomizing trials, this could have implications for treatment of other childhood malignancies and other sarcomas in all ages.

Finally, metastatic disease or unresectable recurrent disease demands another approach. The only option is chemotherapy, as most patients have had RT before [46]. However, in those with metastatic spread, the benefit of chemotherapy is more often limited to extending progression-free survival [25, 26, 33]. Durable responses remain elusive. El Weshi et al.

conclude in their study that an etoposide, ifosfamide and cisplatin combination is active in patients with recurrent/refractory ET, with acceptable toxicity, and offering good palliation [47]. In another pilot study by Felgenhauer et al., the addition of low-dose anti-angiogenic chemotherapy to the standard multiagent chemotherapy in patients with metastatic disease led to an overall 24-month event-free survival of 35 % [48]. However, the recent Euro-Ewing 99 Trial demonstrated that patients with primary disseminated multifocal ESs may survive with intensive multimodal therapy [49].

Prognosis

The prognosis for extraosseous ES appears more favourable than that for ES in bone [6], although prognostic factors of EES seem to be similar to primary bone ES [50]. The outcome for localized extraosseous ES tumours was similar to that reported for all patients with ES treated on protocols at the St. Jude's Children Research Hospital [51]. However, patients with subcutaneous ESFT had a favourable prognosis when compared to their counterparts. Patients with localized disease have estimated 5-year overall survival rates of about 70 % due to considerable progress in both local and systematic therapy during the past four decades [24]. However, a 30 % relapse rate is still unacceptably high, considering that most relapsed patients do not survive. Patients with metastatic or recurrent disease have a worse outcome; 5-year overall survival remains about 25 % [52].

Moreover, studies so far indicate specific predictors for better survival, such as younger age and complete resections [2, 25]. In the recent EURO-Ewing 99 trial, age older than 14 years of age, primary tumour volume over 200 cc and bone marrow or lung metastases were found to be major risk factors for worse prognosis [49]. Finally, 5-year overall survival seems to be superior for localized EES compared to localized skeletal tumours, whereas the hazard ratio for death in patients with localized skeletal tumours compared to localized EES is 2.36 (95 % CI 1.61–3.44) beyond 24 months from initial diagnosis [6].

Conclusions

In conclusion, patient characteristics and outcomes differ among patients with EES compared to patients with skeletal ES. These findings may have important implications for patient care as well, although the main therapeutic strategy is common for all members of the Ewing tumour family. Complete surgery if feasible may be a better option for local disease considering the late side effects of high-dose RT, especially for second malignancy. Anthracycline-based chemotherapy can be used as an adjuvant therapy, and the role of adjuvant local radiotherapy after complete resection is still inconclusive, although it has been shown to improve survival. Neoadjuvant chemotherapy seems to achieve more promising results.

Acknowledgments There were no acknowledgments.

Compliance with Ethical Standards

Conflict of Interest Authors declare that they have conflict of interest.

References

1. Paoletti H, Colineau X, Acalet L et al (1999) Ewing's sarcoma of the soft tissues: apropos of 3 cases and review of the literature. J Radiol 80:477–482
2. Ahmad R, Mayol BR, Davis M, Rougraff BT (1999) Extraskeletal Ewing's sarcoma. Cancer 85:725–731
3. Cheung CC, Kandel RA, Bell RS, Mathews RE, Ghazarian MD (2001) (2001) Extraskeletal Ewing sarcoma in a in a 77-year-old woman. Arch Pathol Lab Med 125:1358–1360
4. Geens L, Van Robays J, Geert V, Van der Speeten K (2013) An unusual location of extraosseous Ewing's sarcoma. Case Rep Oncol 6:293–302
5. Maheshwari V, Siddiqui F, Adreena K, Sherwani RK, Jain A, Alam K (2009) Extraskeletal Ewing's sarcoma—a case report. Internet J Orthop Surg 14:1
6. Applebaum MA, Worch J, Matthay KK et al (2011) Clinical features and outcomes in patients with extraskeletal Ewing sarcoma. Cancer 117:3027–3032
7. O'Keeffe F, Lorigan JG, Wallace S (1990) Radiological features of extraskeletal Ewing sarcoma. Br J Radiol 63:456–460
8. Shirkhoda A, Peuchot M (1989) Extraosseous Ewing's sarcoma. Computed tomography evaluation before and after chemotherapy. Clin Imaging 13:142–146
9. Vanel D, Contsso G, Couanet D et al (1982) Computed tomography in the evaluation of 41 cases of Ewing's sarcoma. Skelet Radiol 9: 8–13
10. Frouge C, Vanel D, Coffre C et al (1988) The role of magnetic resonance imaging in the evaluation of Ewing sarcoma. Skelet Radiol 17:387–392
11. Pinto A, Dickman P, Parham D (2011) Pathobiologic markers of the Ewing Sarcoma family of tumors: state of the art and prediction of behaviour. Sarcoma Article ID 856190
12. Buch AC, Panicker N, Sarawagi S, Anwekar S, Kharat AT (2010) Fine needle aspiration cytology diagnosis of paravertebral extraosseous Ewing's sarcoma. J Cytol 27:146–148
13. Delattre O, Zucman J, Melot T et al (1994) The Ewing family of tumors—a subgroup of small-round-cell tumors defined by specific chimeric transcripts. N Engl J Med 331:294–299
14. Li Q, Cui W, Abulajiang G et al (2014) Application of immunohistochemistry in the diagnosis of small round blue-cell tumors of soft tissue. Clin Lab 60:1383–1392
15. Antonescu C (2014) Round cell sarcomas beyond Ewing: emerging entities. Histopathology 64:26–37
16. Sorensen PH, Liu XF, Delattre O et al (1993) Reverse transcriptase PCR amplification of EWS/FLI-1 fusion transcripts as a diagnostic test for peripheral primitive neuroectodermal tumors of childhood. Diagn Mol Pathol 2:147–157

17. Lewis TB, Coffin CM, Bernard PS (2007) Differentiating Ewing's sarcoma from other round blue-cell tumors using a RT-PCR translocation panel on formalin-fixed paraffin-embedded tissues. Mod Pathol 20:397–404
18. Sumegi J, Nishio J, Nelson M, Frayer RW, Perry D, Bridge JA (2011) A novel t(4;22)(q31;q12) produces an EWSR1-SMARCA5 fusion in extraskeletal Ewing sarcoma/primitive neuroectodermal tumor. Mod Pathol 24:333–342
19. Romeo S, Dei Tos AP (2010) Soft tissue tumors associated with EWSR1 translocation. Virchows Arch 456:219–234
20. Douglas D, Hsu JH, Hung L et al (2008) BMI-1 promotes Ewing sarcoma tumorigenicity independent of CDKN2A repression. Cancer Res 68:6507–6515
21. Avigad S, Cohen IJ, Zilberstein J et al (2004) The predictive potential of molecular detection in the nonmetastatic Ewing family of tumors. Cancer 100:1053–1058
22. Jahromi MS, Jones KB, Schiffman JD (2011) Copy number alterations and methylation in Ewing's sarcoma. Sarcoma Article ID 362173
23. Shukla N, Schiffman J, Reed D, COG Ewing Sarcoma Biology Committee et al (2013) Biomarkers in Ewing sarcoma: the promise and challenge of personalized medicine. A report from the Children's Oncology Group. Front Oncol 6(3):141
24. Biermann JS (2013) Updates in the treatment of bone cancer. J Natl Compr Cancer Netw 11:681–683
25. Rud NP, Reiman HM, Pritchard DJ, Frassica FJ, Smithson WA (1989) Extraosseous Ewing's sarcoma. A study of 42 cases. Cancer 64:1548–1553
26. Covelli HD, Beekman JF, Kingry RL (1980) Extraskeletal Ewing's sarcoma: prolonged survival with recurrence after operation. South Med J 73:1294–1295
27. Qureshi SS, Laskar S, Kembhavi S et al (2013) Extraskeletal Ewing sarcoma in children and adolescents: impact of narrow but negative surgical margin. Pediatr Surg Int 29:1303–1309
28. Paulussen M, Ahrens S, Dunst J et al (2001) Localized Ewing tumor of bone: final results of the cooperative Ewing's sarcoma study CESS 86. J Clin Oncol 19:1818–1829
29. Balamuth NJ, Womer RB (2010) Ewing's sarcoma. Lancet Oncol 11:184–192
30. Dunst J, Schuck A (2004) Role of radiotherapy in Ewing tumors. Pediatr Blood Cancer 42:465–470
31. Vogin G, Helfre S, Glorion C et al (2013) Local control and sequelae in localised Ewing tumours of the spine: a French retrospective study. Eur J Cancer 49:1314–1323
32. Bernstein M, Kovar H, Paulussen M et al (2006) Ewing's sarcoma family of tumors: current management. Oncologist 11:503–519
33. Schuck A, Ahrens S, Paulussen M et al (2003) Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys 55:168–177
34. Iwata S, Yonemoto T, Ishii T, Kumagai K et al (2013) Efficacy of carbon-ion radiotherapy and high-dose chemotherapy for patients with unresectable Ewing's sarcoma family of tumors. Int J Clin Oncol 18:1114–1118
35. Bacci G, Balladelli A, Forni C et al (2007) Adjuvant and neoadjuvant chemotherapy for Ewing sarcoma family tumors in patients aged between 40 and 60: report of 35 cases and comparison of results with 586 younger patients treated with the same protocols in the same years. Cancer 109:780–786
36. Castex MP, Rubie H, Stevens MC et al (2007) Extraosseous localized Ewing tumors: improved outcome with anthracyclines—the French Society of Pediatric Oncology and International Society of Pediatric Oncology. J Clin Oncol 25:1176–1182
37. Raney RB, Asmar L, Newton WA Jr et al (1997) Ewing's sarcoma of soft tissues in childhood: a report from the Intergroup Rhabdomyosarcoma Study, 1972–1991. J Clin Oncol 15:574–582
38. Shamberger RC, LaQuaglia MP, Gebhardt MC et al (2003) Ewing sarcoma/primitive neuroectodermal tumor of the chest wall: impact of initial versus delayed resection on tumor margins, survival, and use of radiation therapy. Ann Surg 238:563–567
39. Krasin MJ, Davidoff AM, Rodriguez-Galindo C et al (2005) Definitive surgery and multiagent systemic therapy for patients with localized Ewing sarcoma family of tumors: local outcome and prognostic factors. Cancer 104:367–373
40. Kinsella TJ, Triche TJ, Dickman PS, Costa J, Tepper JE, Glaubiger D (1983) Extraskeletal Ewing's sarcoma: results of combined modality treatment. J Clin Oncol 1:489–495
41. Grier HE, Krailo MD, Tarbell NJ et al (2003) Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 348:694–701
42. Tao HT, Hu Y, Wang JL et al (2013) Extraskeletal Ewing sarcomas in late adolescence and adults: a study of 37 patients. Asian Pac J Cancer Prev 14:2967–2971
43. Womer RB, West DC, Krailo M et al (2012) Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol 30:4148–4154
44. Paulussen M, Craft AW, Lewis I et al (2008) Results of the EICESS-92 study: two randomized trials of Ewing's sarcoma treatment—cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol 26:4385–4393
45. DuBois SG, Grier HE (2009) Chemotherapy: the role of ifosfamide and etoposide in Ewing sarcoma. Nat Rev Clin Oncol 6:251–253
46. Evans R, Nesbit M, Askin F (1985) Local recurrence, rate and sites of metastases, and time to relapse as a function of treatment regimen, size of primary and surgical history in 62 patients presenting with non-metastatic Ewing's sarcoma of the pelvic bones. Int J Radiat Oncol Biol Phys 11:129–136
47. El Weshi A, Memon M, Raja M et al (2004) VIP (etoposide, ifosfamide, cisplatin) in adult patients with recurrent or refractory Ewing sarcoma family of tumors. Am J Clin Oncol 27:529–534
48. Felgenhauer JL, Nieder ML, Krailo MD et al (2013) A pilot study of low-dose anti-angiogenic chemotherapy in combination with standard multiagent chemotherapy for patients with newly diagnosed metastatic Ewing sarcoma family of tumors: a Children's Oncology Group (COG) Phase II study NCT00061893. Pediatr Blood Cancer 60:409–414
49. Ladenstein R, Pötschger U, Le Deley MC et al (2010) Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol 28:3284–3291
50. Tural D, Molinas Mandel N, Dervisoglu S et al (2012) Extraskeletal Ewing's sarcoma family of tumors in adults: prognostic factors and clinical outcome. Jpn J Clin Oncol 42:420–426
51. Shannon OW, Denbo JW, Billups CA et al (2012) Analysis of prognostic factors in extraosseous Ewing sarcoma family of tumors: review of St. Jude Children's research hospital experience. Ann Surg Oncol 19:3816–3822
52. Lee J, Hoang BH, Ziogas A, Zell JA (2010) Analysis of prognostic factors in Ewing sarcoma using a population based cancer registry. Cancer 116:1964–1973