

RESEARCH ARTICLE

Extraskelatal Ewing Sarcomas in Late Adolescence and Adults: A Study of 37 Patients

Hai-Tao Tao^{1,2}, Yi Hu^{1*}, Jin-Liang Wang¹, Yao Cheng^{1,2}, Xin Zhang¹, Huan Wang¹, Su-Jie Zhang¹

Abstract

Background: Extraskelatal Ewing sarcoma (EES)/primitive neuroectodermal tumours (PNET) are rare soft tissue sarcomas. Prognostic factors and optimal therapy are still unconfirmed. **Materials and Methods:** We performed a retrospective analysis on patients to explore the clinic characteristics and prognostic factors of this rare disease. A total of 37 patients older than 15 years referred to our institute from Jan., 2002 to Jan., 2012 were reviewed. The characteristics, treatment and outcome were collected and analyzed. **Results:** The median age was 28 years (range 15-65); the median size of primary tumours was 8.2 cm (range 2-19). Sixteen patients (43%) had metastatic disease at the initial presentation. Wide surgical margins were achieved in 14 cases (38%). Anthracycline or platinum-based chemotherapy was performed on 29 patients (74%). Radiotherapy was delivered in 13 (35%). At a median follow-up visit of 24 months (range 2-81), the media event-free survival (EFS) and overall survival (OS) were 15.8 and 30.2 months, respectively. The 3-year EFS and OS rates were 24% and 43%, respectively. Metastases at presentation and wide surgical margins were significantly associated with OS and EFS. Tumour size was significantly associated with OS but not EFS. There were no significant differences between anthracycline and platinum based chemotherapy regarding EFS and OS. **Conclusions:** EES/PNET is a malignant tumour with high recurrence and frequent distant metastasis. Multimodality therapy featuring wide surgical margins, aggressive chemotherapy and adjuvant local radiotherapy is necessary for this rare disease. Platinum-based chemotherapy can be used as an adjuvant therapy.

Keywords: Ewing sarcoma - extraskelatal - extraosseous - PNET - survival

Asian Pacific J Cancer Prev, 14 (5), 2967-2971

Introduction

The Ewing sarcoma family of tumours (ESFT) consists of a group of tumours including classic Ewing sarcoma of bone, Askin tumours of the chest wall, Extraskelatal Ewing sarcoma (EES) and primitive neuroectodermal tumours of bone or soft tissues (Maheshwari et al., 2010). Although rare, such tumours constitute the second most frequent sarcoma of bone in child and adolescents (Herzog, 2005). These small round cell tumours are considered to be the same tumour family because they all share a common neural histogenesis and tumour genetics. Approximately 95% of patients with ESFT have a characteristic t (11; 22) (q24; q12) or t (21; 22) (q22; q12) chromosomal translocation, which results in fusion of the EWS gene on chromosome 22 and the FLI-1 gene on chromosome 11 or the ERG gene on chromosome 21 (Downing et al., 1993; Torchia et al., 2003). EES was first described by Tefft in 1969. He reported four patients who had paravertebral soft tissue tumours with a histologic appearance resembling Ewing sarcoma (Tefft et al., 1969), EES/PNET is usually

seen in the second or third decades and can be developed from soft tissues in any location, the most common sites are extremities, trunk, and retroperitoneum (Raney et al., 1997; Maheshwari et al., 2010).

Since 1970s, Kinsella et al first reported a series of patients with EES treated with standard combined-modality therapy, much progress has been developed, especially in the methodology of diagnosis and molecular characterization, but treatment and outcome still need to be explored (Kinsella et al., 1983; Zagar et al., 2008). Several studies have demonstrated the prognostic impacts on tumour stages (localized vs metastatic), sizes, surgical margins, high lactate dehydrogenase, present of CR to initial treatment (Kinsella et al., 1983; Rud et al., 1989; Raney et al., 1997; Ahmad et al., 1999; Eralp et al., 2002; El et al., 2010; Applebaum et al., 2011; Shannon et al., 2012; Tural et al., 2012).

However, a small number of patients were limited much information about clinical features, therapeutic approaches and prognostic factors, and most studies focused on African or white people, but very rarely on

¹Department of Oncology, China PLA General Hospital, Beijing, ²School of Medicine, Nankai University, TianJin, China *For correspondence: huyi0401@yahoo.com.cn

Asian patients.

In this study, we carried out a retrospective review of patients with EES/PNET treated in PLA Hospital in China. Our aims were to report clinical and treatment characteristics, to explore the factors as predictors of outcomes in patients with EES/PNET.

Materials and Methods

We identified 37 patients with EES/PNET from a retrospective database in PLA hospital from Jan., 2002 to Jan., 2012. The diagnosis of all cases was based on biopsy specimens or surgery samples, which were reviewed by a senior pathologist in our centre. Each diagnosis was established on the basis of the presence of small round cells, with positive CD99 and no cytological, histological or immunohistochemical features of lymphoma, rhabdomyosarcoma or neuroblastoma. The detection method of characteristic chromosomal translocations by reverse transcriptase polymerase chain reaction (RT-PCR) became available in 1993, but was not routinely performed in this series. The following characteristics were collected from the patient charts: age, gender, tumour size and location of primary tumours, presence and location of metastases. In addition, treatment modalities (cytotoxic agents, number of chemotherapy cycles, surgery, radiotherapy, other treatment), treatment outcomes (response, progression), time to progression, time to death or end of follow-up visit were recorded.

The follow-up visit was up to Sep., 2012. All the patients were investigated by phone and the out-patient data were also useful. In our department, patients were evaluated every 3 months for 2 years, every 6 months between 2–5 years and annually thereafter. Evaluation included physical examination, serum chemistries and blood counts, with thoracic CT and radionuclide bone scan. The diagnosis of recurrence was made on the basis of physical examination, imaging and pathology, if required.

Overall survival (OS) and event-free survival (EFS) were estimated using Kaplan-Meier method together with 95% confidence intervals. A univariate analysis was carried out to assess if any prognostic variables conferred an improved survivor-ship. OS was calculated from the date of diagnosis to the date of death. EFS was calculated from date of diagnosis to date of the first event (relapsed or progressive disease, second malignancy, or death). EFS and OS were censored at the patient's last contact date. Chi square test was used to evaluate the differences between local controls. $P < 0.05$ was considered statistically significant and all p values correspond to two-sided significance tests.

Results

Patients' characteristics

Thirty-seven patients with EES/PNET were followed up in our institute during ten years between 2002 and 2012. Two out of them were referred for local or metastatic relapse after surgical resection alone as primary treatment. The rest were referred for initial treatment. Thirteen patients were females (35%), and 24 males (65%). The

median age was 28 years (range 15-65). In 8 patients (22%), the tumour was located at an extremity, whereas in 29 patients (78%), tumours were located at central locations, including the head and neck region. The median tumour size at diagnosis was 8.2 cm (range 2–19 cm). Tumour size was larger than 10 cm in 14 patients (38%), and one was unknown due to lack of exact information. Twenty-one patients (57%) had regionally confined tumour (M0), 16 patients (43%) had metastatic disease (M1), and 6 of them were involved more than one site.

Treatment

The treatment plan given to the patients depended on the stage of disease. Eighteen patients (86%) with localized disease received surgery as part of their disease's local control, while 3 ones with localized disease didn't received surgery because of extensive invasion. One of them had tumour in the prostate. Magnetic Resonance (MR) showed the tumour invaded the surrounding tissues, radical resection was impossible. The patient received 6 cycles' chemotherapy and radical radiation therapy, the local disease was stable for 18 months, but he got distant metastasis in the lung later. Ten patients (62%) with disseminated disease received surgery, 6 of them received palliative surgery. Of note, 1 of 4 patients who received radical resection of primary tumour had metastatic disease in the brain. Unfortunately, the metastatic tumour wasn't found before surgery; the patient died 2 months after surgery.

Radiation treatment was given in 13 patients, 7 of them got localized disease and received a median total dose of 54 Gy (48-64 Gy) at 1.8 Gy daily dose. The planning target volume encompassed the prechemotherapy tumour volume plus a minimum of 2.5 cm margins all around. Indications for postoperative radiotherapy included gross residual disease and positive or close resection margins. Six patients (16%) received palliative radiation for locoregional tumour, and 26 ones (70%) didn't receive any radiation therapy in the primary treatment.

No standard treatment model has established for EES/PNET, and the management is different in different clinic centres. In this series, two regimens were routinely applied in clinical practice. One is anthracycline based chemotherapy (13 patients, 45%): doxorubicin 50 mg/m² in addition to vincristine given at 1.4 mg/m² and cyclophosphamide given at 1,200 mg/m² (VAC) with 3 weekly intervals, doxorubicin was replaced by actinomycin D (1.25 mg/m²) after reaching a cumulative dose of 450 mg/m² or couldn't been tolerated by patients. Of this regimen, administration was given three cycles every 3 weeks before surgery, and 9 cycles for postoperation. The other is platinum-based chemotherapy (16 patients, 55%): cisplatin in 75 mg/m² in addition with etoposide 100 mg/m² for 5 days with 3 weekly intervals. In 9 patients, the cisplatin was changed to carboplatin. In one patient the etoposide was replaced by paclitaxel, and in another 2 patients bleomycin was added because of good tolerance. Of this regimen, administration was given 6 cycles at least, then etoposide capsules was given as maintenance therapy or best support care was given. The media chemotherapy cycles was 5 (range 1-13). All patients received G-CSF

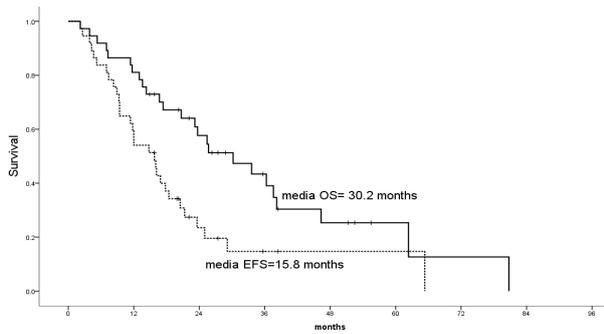


Figure 1. OS and EFS

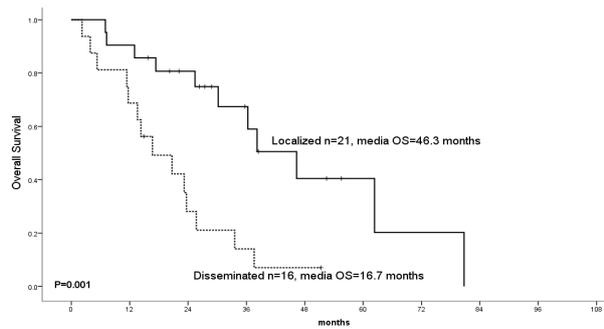


Figure 2. OS According to Tumour Extent

support after chemotherapy.

Local control

All patients but one with localized disease were evaluated for local control, the patient was excluded because she refused to further treatment after the first cycle of chemotherapy and interventional therapy due to poor karnofsky performance status (KPS). A total of 12 (60%) patients got local recurrence with or without distant recurrence, 2 patients got distant recurrence alone, and 6 patients were event-free. The median time to local recurrence was 18.1 months (range 4.3-65). Six patients received both surgery and radiotherapy with or without chemotherapy for local control, 3 (50%) of them got local recurrence. Fourteen patients received surgery or radiotherapy, and 9 (64%) got local recurrence. Difference in the local recurrence rate was not statistically significant ($P>0.05$). In our study, 12 patients had resection with wide margins (>2.5 cm) and 6 patients had positive surgical margins. Local recurrence rate was higher for patients with positive surgical margins (83%) compared with patients with wide surgical margins (50%) but with no significant difference due to the limit number of patients ($P>0.05$).

Outcome and analysis

As of Sep., 2012, with a median follow-up visit of 24 months (range 2–81 months), 12 (32%) of the patients were alive and 7 (19%) were disease-free; First events included relapsed or progressive disease in 26 patients (13 local, 10 distant, three simultaneous local/distant) and death in 4 patients. All deaths but one were attributed to disease progression. The patient with brain metastasis received resection of primary tumour but died just two months later. The median follow-up time for 12 censored patients in this data set was 29 months (range 15–56). No second cancer had been reported so far in this series of

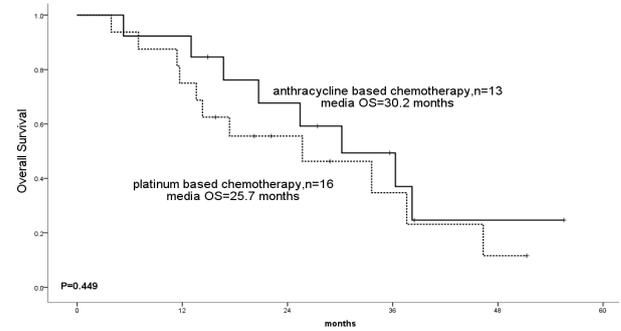


Figure 3. OS According to Chemotherapeutic Agents

patients.

The median EFS and OS for the entire group were 15.8 months and 30.2 months, respectively (Figure 1). The 1-year, 3-year and 5-year EFS rates were 57%, 24% and 0%, respectively. The 1-year, 3-year and 5-year OS rates were 81%, 43% and 11%, respectively. Of note, the median EFS was significantly less satisfied in metastatic disease compared with patients with localized disease (9.4 vs 18.4, $P=0.007$) as well as OS (16.7 vs 46.3, $P=0.001$, Figure 2).

Presentation with localized disease ($P=0.007$), adequate surgical margins ($P=0.000$) were associated with a significantly long EFS. Significant predictors of better OS at univariate analysis were tumour size 10 cm ($P=0.032$), localized disease ($P=0.001$) and wide surgical margin ($P=0.002$). Factors including gender (male vs female), age (20 vs >20 years), primary tumour site (central vs extremity), and radiotherapy (yes vs no) were not shown to have a significant association with EFS or OS. Tumour size had a significant effect on OS instead of EFS. Current standard chemotherapeutic agents for EFST is vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide (Grier et al., 2003), but in our institute, both anthracycline based chemotherapy and platinum-based chemotherapy are routinely used, the analysis show no differences regarding EFS and OS (Figure 3).

Discussion

Sarcoma is not a rare disease (Lasrado et al., 2012; Ibrahim et al., 2013; Sun et al., 2013; Zhang et al, 2013). However, patients with EES are less common. Since Tefft first described 4 patients with EES, several series of patients was reported, the largest prospective collection of patients studied to date with EES/PNET were from IRS trials. 5% of nearly 3,000 patients on these IRS trials (total of 130) had EES/PNET (Raney et al., 1997). The clinical features, treatment and prognostic factors of EES/PNET are limited to small reports from few institutes due to the rarity of this disease, and little data about the Asian patients could be found. It has been reported that EES is relatively more common in adults (El et al., 2010). Our series focused on late adolescents and adult patients with EES/PNET, and was the first report of Asian. The median age at diagnosis in our patients was 28 years, whereas other previous studies' median age was 20-26 years (Rud et al., 1989; Baldini et al., 1999; Eralp et al., 2002; El et al., 2010; Tural et al., 2012). 65% of the patients in the study were

men. ESFT is more common in males than in females, with a reported ratio of 1.3 to 1.5:1 (Maheshwari et al., 2010), but no sexual predominance of EES/PNET was existence in published reports. The predominant location of EES in our series was the trunk. Previous studies also showed more frequent trunk localization for EES (Raney et al., 1997; El et al., 2010; Tural et al., 2012). However, Locations in the extremities were also observed in some other reports (Rud et al., 1989; Kaspers et al., 1991). The median tumour size of this series is 8.2 cm, which is similar to other reported series presenting a range of 6.5-11 cm, but the incidence of distant metastases in our series is the highest reported in published studies, nearly half of patients got metastatic disease (Rud et al., 1989; Baldini et al., 1999; El et al., 2010; Shannon et al., 2012; Tural et al., 2012). Those difficult cases are more likely to send to our hospital, what makes selection bias. EFST has a strong potential to metastasize. More than 10% of patients present with multiple bone metastases at initial diagnosis (Maheshwari et al., 2010). The most metastatic organs are the lung, bone, lymph node, or a combination, but metastases in the liver or brain are rare and malignant. Patients with brain metastasis got the mean OS of 5.1 months (19), we reported a patient with brain metastasis and survival for only 2 months.

Combined modality therapy was established as the basic treatment for ESFT for a long time (Kinsella et al., 1983). Although the fact that all EFST share a common genetic basis, there is still some debate about whether we should use the same therapeutic approach as with classic Ewing sarcoma of bone (Zagar et al., 2008). Recently, two researches have confirmed that patients with EES fare well with the same tumour characteristics and treatment as with ESFT (Gururangan et al., 1998; Shannon et al., 2012). It is widely recognized that EFST are, indeed, systemic diseases at presentation, even if documented metastases are not found (Zagar et al., 2008). The application of adjuvant chemotherapy, which began in the early of 1970s, has greatly improved survival rates for patients with localized ESFT, from about 10% to 70-80% (Balamuth et al., 2010). Nearly every chemotherapy protocol for Ewing sarcoma has been based on four drugs: doxorubicin, cyclophosphamide, vincristine, and dactinomycin. Then the study INT-0091 showed that ifosfamide and etoposide (IE), alternating with the standard regimen of those drugs markedly improved both OS and EFS for patients with localized tumours (Grier et al., 2003). The regimen of alternating VDC-IE every 2 weeks has become standard for North American patients with ESFT; however, there is no standard chemotherapy regimen available in this context until now. In our institute, VDC-IE protocol was routinely performed on children and young adolescents, platinum-based chemotherapy was also performed on adults. EES/PNET belongs to small round cell tumour, and sometimes has neural differentiation, especially for PNET. Platinum-based chemotherapy was performed on many kinds of solid tumour. Several researches has explored the safety and efficacy of platinum-based chemotherapy (El et al., 2004; Whelan et al., 2004; Owens et al., 2013), Patients with refractory Ewing sarcoma family tumours were enrolled and received platinum-

based chemotherapy, the results demonstrated the regimen was well tolerated and offered well palliation, suggesting the probability as the first-line treatment in this disease (El et al., 2004). Median EFS and OS for anthracycline based chemotherapy and platinum-based chemotherapy were 16.0 vs 11.4 ($P=0.366$), 30.2 vs 25.7 ($P=0.449$), respectively, suggesting platinum-based chemotherapy can be used as the adjuvant therapy.

Currently, treatment is focused on the goal of eradicating micrometastases and reducing the size of primary tumours so as to achieve better tumour demarcation and improve the success of local control. The exact indications for local control in the form of surgical resection and/or RT are controversial, because there were no trials comparing radiotherapy with surgery. Careful patient selection with surgery has led to local failure rates of <10% (Maheshwari et al., 2010). Surgery affords local control and may prevent the late recurrence of chemo-resistant cells. Another potential benefit with surgical resection of primary tumors is the opportunity of gather information concerning the amount of necrosis in the resected tumors. Patients with residual viable tumors in the resected specimen have a worse outcome than patients with complete necrosis (Oberlin et al., 2001; El et al., 2010). Several studies has conformed that the surgical margin would be an appropriate option for local control (Rud et al., 1989; Eralp et al., 2002; El et al., 2010; Tural et al., 2012). Our study also showed that patients with wide surgical margin got better EFS and OS, but no difference was shown between the patients with positive surgical margins and with no surgery. The primary tumors in 12 patients with positive surgical margins mainly were located in the trunk, abdomen or pelvis. It's difficulty for those to get a radical resection. Hence, the surgery should be used judiciously in those patients since a lack of definitive benefit.

Radiation for local control is recommended for unresectable tumors, and when there is a low likelihood that adequate surgical margins can be achieved. Radiotherapy may also have a role in improving local disease control in patients with poor chemotherapeutic response (Dunst et al., 2004). Only 13 patients (35.1%) in our study received radiotherapy and 8 was performed in localized disease, the local control was not so satisfied in this series comparing with others studies (Raney et al., 1997; Gururangan et al., 1998; El et al., 2010; Applebaum et al., 2011; Shannon et al., 2012; Tural et al., 2012), the median time to local recurrence was 18.1 months, 60% of the patients with localized disease got recurrence and only 6 patients (30%) with no progression. Most of our cases (64%) had truck lesions and radical surgery was difficult. The adjuvant radiotherapy seems necessary to patients in those high-risk lesion (Dunst et al., 2004).

In our study, tumour size, metastatic disease at presentation and the surgical resection margin were the most important factors significantly influencing treatment outcome on univariate analysis. This finding is similar to most of the literature reporting either on EES (Rud et al., 1989; Raney et al., 1997; Eralp et al., 2002; El et al., 2010; Applebaum et al., 2011; Shannon et al., 2012; Tural et al., 2012). But due to the rarity of this tumour,

most of the reported literatures regarding EES are from single-institute retrospective case reviews. Large number of patients studied on multicentre randomized controlled clinical trials are necessary to form new treatments.

In conclusion, it is the first report about extraskelatal Ewing sarcoma (EES)/primitive neuroectodermal tumour in Asian, which is an aggressive type of tumour with high recurrence incidence and distant metastasis. This series showed that metastases at presentation and wide surgical margins are the most important prognostic factors. Multimodality therapy composed of wide surgical margins, aggressive chemotherapy and adjuvant local radiation therapy is necessary for this rare disease. Platinum-based chemotherapy can also be used as the adjuvant therapy.

References

- Ahmad R, Mayol BR, Davis M, et al (1999). Extraskelatal Ewing's sarcoma. *Cancer*, **85**, 725-31.
- Applebaum MA, Worch J, Matthay KK, et al (2011). Clinical features and outcomes in patients with extraskelatal Ewing sarcoma. *Cancer*, **117**, 3027-32.
- Balamuth NJ, Womer RB (2010). Ewing's sarcoma. *Lancet Oncol*, **11**, 184-92.
- Baldini EH, Demetri GD, Fletcher CD, et al (1999). Adults with Ewing's sarcoma/primitive neuroectodermal tumour: adverse effect of older age and primary extraosseous disease on outcome. *Ann Surg*, **230**, 79-86.
- Downing JR, Head DR, Parham DM, et al (1993). Detection of the (11; 22) (q24;q12) translocation of Ewing's sarcoma and peripheral neuroectodermal tumour by reverse transcription polymerase chain reaction. *Am J Pathol*, **143**, 1294-300.
- Dunst J, Schuck A (2004). Role of radiotherapy in Ewing tumours. *Pediatr Blood Cancer*, **42**, 465-70.
- El Weshi A, Allam A, Ajarim D, et al (2010). Extraskelatal Ewing's sarcoma family of tumours in adults: analysis of 57 patients from a single institute. *Clin Oncol (R Coll Radiol)*, **22**, 374-81.
- 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 tumours. *Am J Clin Oncol*, **27**, 529-34.
- Eralp Y, Baybek S, Basaran M, et al (2002). Prognostic factors and survival in late adolescent and adult patients with small round cell tumours. *Am J Clin Oncol*, **25**, 418-24.
- Grier HE, Krailo MD, Tarbell NJ, et al (2003). Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumour of bone. *N Engl J Med*, **348**, 694-701.
- Gururangan S, Marina NM, Luo X, et al (1998). Treatment of children with peripheral primitive neuroectodermal tumour or extraosseous Ewing's tumour with Ewing's-directed therapy. *J Pediatr Hematol Oncol*, **20**, 55-61.
- Herzog CE (2005). Overview of sarcomas in the adolescent and young adult population. *J Pediatr Hematol Oncol*, **27**, 215-8.
- Ibrahim N, Abou-Elela E, Darwish D (2013). Survival of mesothelioma in a palliative medical care unit in egypt. *Asian Pac J Cancer Prev*, **14**, 739-42.
- Kaspers GJ, Kamphorst W, van de Graaff M, et al (1991). Primary spinal epidural extraosseous Ewing's sarcoma. *Cancer*, **68**, 648-54.
- Kinsella TJ, Triche TJ, Dickman PS, et al (1983). Extraskelatal Ewing's sarcoma: results of combined modality treatment. *J Clin Oncol*, **1**, 489-95.
- Lasrado S, Prabhu P, Kakria A, et al (2012). Clinicopathological profile of head and neck cancers in the Western development region, Nepal: a 4-year snapshot. *Asian Pac J Cancer Prev*, **13**, 6059-62.
- Maheshwari AV, Cheng EY (2010). Ewing sarcoma family of tumours. *J Am Acad Orthop Surg*, **18**, 94-107.
- Oberlin O, Deley MC, Bui BN, et al (2001). Prognostic factors in localized Ewing's tumours and peripheral neuroectodermal tumours: the third study of the French Society of Paediatric Oncology (EW88 study). *Br J Cancer*, **85**, 1646-54.
- Ogose A, Morita T, Hotta T, et al (1999). Brain metastases in musculoskeletal sarcomas. *Jpn J Clin Oncol*, **29**, 245-7.
- Owens C, Laurence V, Benboubker L, et al (2013). Phase II study of cisplatin and oral VP16 in patients with refractory or relapsed Ewing sarcoma. *Cancer Chemother Pharmacol*, **71**, 399-404.
- Raney RB, Asmar L, Newton WA, et al (1997). Ewing's sarcoma of soft tissues in childhood: a report from the Intergroup Rhabdomyosarcoma Study, 1972 to 1991. *J Clin Oncol*, **15**, 574-82.
- Rud NP, Reiman HM, Pritchard DJ, et al (1989). Extraosseous Ewing's sarcoma: a study of 42 cases. *Cancer*, **64**, 1548-53.
- Shannon Orr W, Denbo JW, Billups CA, et al (2012). Analysis of prognostic factors in extraosseous Ewing sarcoma family of tumours: review of St. Jude Children's Research Hospital experience. *Ann Surg Oncol*, **19**, 3816-22.
- Sun XH, Hou WG, Zhao HX, et al (2013). Single Nucleotide Polymorphisms in the NER Pathway and Clinical Outcome of Patients with Bone Malignant Tumors. *Asian Pac J Cancer Prev*, **14**, 2049-52.
- Tefft M, Vawter GF, Mitus A (1969). Paravertebral "round cell" tumours in children. *Radiology*, **92**, 1501-9.
- Torchia EC, Jaishankar S, Baker SJ (2003). Ewing tumour fusion proteins block the differentiation of pluripotent marrow stromal cells. *Cancer Res*, **63**, 3464-8.
- Tural D, Molinas Mandel N, Dervisoglu S, et al (2012). Extraskelatal Ewing's sarcoma family of tumours in adults: prognostic factors and clinical outcome. *Jpn J Clin Oncol*, **42**, 420-6.
- Whelan JS, McTiernan A, Kakouri E, et al (2004). Carboplatin-based chemotherapy for refractory and recurrent Ewing's tumours. *Pediatr Blood Cancer*, **43**, 237-42.
- Zagar TM, Triche TJ, Kinsella TJ (2008). Extraosseous Ewing's sarcoma: 25 years later. *J Clin Oncol*, **26**, 4230-2.
- Zhang Q, Geng PL, Yin P, et al (2013). Down-regulation of long non-coding RNA TUG1 inhibits osteosarcoma cell proliferation and promotes apoptosis. *Asian Pac J Cancer Prev*, **14**, 2311-5.