Original Article

Ewing's sarcoma in pediatrics and adults: Outcomes by multimodality approach

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ABSTRACT

Background: To review the clinical characteristics and outcomes of patients with Ewing's sarcoma (EWS) treated at our institute with radiation, chemotherapy, and surgery. **Materials and Methods:** Patients of EWS treated between January 2009 and December 2014 were retrospectively analyzed. Multimodality treatment with chemotherapy, radiation, and/or surgery has been used. Pattern of failure, locoregional control rates, and disease-free survival (DFS) was estimated using Kaplan–Meier method. Univariate and multivariate analysis was done to identify various poor prognostic factors for local control and survival. **Results:** Eighty-three patients were reviewed. Eleven patients (13.2%) had metastatic disease at presentation, out of which 7 (8.4%) had lung metastasis. The most frequent location was extremities (53%), followed by ribs, clavicle, and scapula (18.1%), axial site (10.8%), pelvis (7.2%), extraosseous site (6%), and skull (4.8%). The median follow-up period was 16 months. Out of 72 patients with localized disease, 37 (44.6%) patients failed the treatment. The most common site of distant failure was lung (18.1%), followed by bone (10.8%) and brain (4.8%). The 1 year, 2 years, and 5 years DFS were 73.8%, 45.7%, and 33.2%, respectively. The 1 year, 2 years, and 5 years local control rates were 73.3%, 65.1%, and 55.8%, respectively. The median time to local failure was 10 months. Age >12 years ($P < 0.05$) was found to be the only factor associated with poor prognosis for survival by both univariate and multivariate analysis. Axial site ($P < 0.03$), and chemotherapy regimen with vincristine, adriamycin (doxorubicin), cyclophosphamide only ($P < 0.03$) were found to be associated with a poor prognosis for local control by univariate analysis. By multivariate analysis, however, none of the factors were found to be a poor prognostic factor for local control. **Conclusions:** Aggressive combined modality approaches should be considered for all patients with EWS. Survival after progression was dismal.

Key words: Chemotherapy, Ewing's sarcoma, radiotherapy, surgery

INTRODUCTION

Ewing's sarcoma (EWS) is a small round cell tumor, with a characteristic t(11;22)(q24;q12) or t(21;22)(q22;q12) chromosomal translocation seen in 95% of cases.[1] It is the second most common tumor of the bone in children and constitutes about 2% of all pediatric malignancies.[2,3] The median age at presentation is 15 years.[4] Bone is the most common primary site of disease. The poorest prognostic factor identified so far is the metastatic disease at presentation. Other factors include pulmonary site of metastases, age older than 12, axial site of primary disease, and response to chemotherapy.[5]

The treatment of EWS is multimodal based on the combination of chemotherapy with local treatment such as surgery or radiotherapy. Increments in 5 years survival rates of only 15–20% to approximately 60–70% nowadays have been seen by the addition of newer chemotherapeutic regimens and advanced radiotherapy techniques.[6-10] The progression-free survival rates are approximately 25% for disseminated disease and 80% for localized disease.[11]

Most treatment protocols include high-dose alkylating agents, anthracyclines, and etoposide, but the optimal

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Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.180772

Cite this article as: Kapoor R, Bansal A, Nagpal P. Ewing's sarcoma in pediatrics and adults: Outcomes by multimodality approach. Clin Cancer Investig J 2016;5:224-9.

duration of treatment, dose intensity, and treatment of high-risk patients are still debated. In the recent decades, efforts to improve the outcome of patients with nonmetastatic disease have focused mainly on the schedule and timing of these treatment regimens, with seemingly better results when using dose-intensive regimen.

The aim of this study is to evaluate the clinical characteristics and outcomes of patients with EWS treated at our institute in the last 5 years. Furthermore, various poor prognostic factors influencing local control and survival of the patients have been identified.

MATERIALS AND METHODS

Patient selection

All patients of EWS (localized or metastatic at presentation), who were registered and treated at our institute between the year 2009 and 2014 were analyzed in this study.

Pretreatment evaluation

Diagnosis of all cases was based on biopsy specimens. Staging was based on physical examination, computed tomography (CT) scan, or magnetic resonance imaging scan of the primary tumor, CT scan of the chest, and bone scan. The tumor size was estimated by CT scan measures of the three diameters of the lesion.

Management

All patients were managed by multimodality treatment, which includes chemotherapy, radiation therapy, and/or surgery when required.

Induction chemotherapy

Induction chemotherapy consisted of 2–3 cycles of vincristine, adriamycin (doxorubicin), cyclophosphamide (VAC) chemotherapy, (V = vincristine 1.5 mg/m^2 as bolus injection [day 1] + A = doxorubicin 60 mg/m^2 in a 4-h infusion [day 1] + C = cyclophosphamide 800 mg/m^2 as bolus injection [day 1]) alternating with ifosfamide-etoposide (IE) chemotherapy, (I = ifosfamide 1000 mg/m^2 in a 1-h infusion [days 1, 2, 3] with 2-mercaptoethanesulfonate sodium at 0, 4, 8 h + E = etoposide 100 mg/m^2 in a 2-h infusion [days 1, 2, and 3]). Cycles were administered at 3-week intervals. Evaluation of response to chemotherapy was performed either by physical examination or imaging, after the induction chemotherapy.

Local treatment

The first choice of local treatment was definitive radiotherapy at our institute. Radiotherapy consisted of radiation to the entire bone or bones containing the original gross tumor volume to a dose of 40–45 Gy, followed by a boost of 10–25 Gy to the lesion with a 2–4-cm margin. Tighter medial margins were occasionally used in the pelvis to spare the bladder and bowel. Radiotherapy was delivered using megavoltage technology, either Co-60 or 6–20 MV photons. Postoperative radiotherapy was given in selected cases according to the rate of necrosis and surgical margins.

Consolidation treatment

Consolidation chemotherapy consisted completing four more cycles of chemotherapy with VAC alternating with IE.

Surgery

Surgery in the form of wide local excision (WLE) was planned as a primary treatment in some patients who had disease at the site where surgery is possible with negative margins, for example, rib, scapula, clavicle, and orbit. Some patients with spinal disease were also managed by laminectomy and gross tumor excision as the primary treatment. WLE was also done in patients who had residual or persistent disease postchemotherapy and radiation.

Amputation was done as a primary treatment in patients with localized large extremity tumors, with compromised neurovascular supply, or as adjuvant treatment in patients who did not respond to neoadjuvant chemotherapy.

For patients with metastatic disease at presentation, six cycles of palliative chemotherapy with either VAC alone or VAC alternating with IE, or ifosfamide, cisplatin, and etoposide (ICE) chemotherapy (C = cisplatin 30 mg/m^2) were planned. Local radiotherapy was given with radical or palliative intent depending on response to chemotherapy.

Response assessment and follow-up

During treatment, the response was evaluated by Response Evaluation Criteria in Solid Tumors criteria[12] by both physical examination and using imaging modalities as used before the start of treatment. Response to chemotherapy was defined as complete response (complete disappearance of the lesion), partial response (at least a 30% decrease in the sum of the longest diameter of target lesion, taking as reference the baseline sum longest diameter), progressive disease (any new lesion or increase in tumor size by at least 20%), and stable disease (neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease).

After treatment, patients were followed by physical checkups, standard radiographs, and CT scan of the chest and local site. Additional studies, including if necessary biopsy, were performed when indicated. Outpatients were followed every 3 months for 2 years and then twice a year.

Statistical analysis

In this retrospective study, frequency tables with counts and percentages were used to describe pretreatment and

treatment characteristics of the patients. Disease-free survival (DFS) and local control rates (LCs) were calculated by the Kaplan–Meier method using statistical software SPSS (Software package used for statistical analysis) 20, IBM, Armonk, NY, United States of America. The relationship between the prognostic factors and survival was assessed by univariate analysis. For multivariate analysis, the Cox proportional hazard model was used. A $P < 0.05$ was taken as statistically significant.

RESULTS

Patient and treatment characteristics

Table 1 shows the profile and treatment details of the patients. Out of 83 patients, with median age of 18 years (range: 3–45 years), 11 (13.3%) patients had metastatic disease at presentation. The most common site of initial metastasis at presentation was lung in seven patients and bone in four patients.

About 47 patients (55.6%) (46 patients with localized disease and one patient with metastatic disease at presentation), were treated by two to three cycles of neoadjuvant chemotherapy with VAC or VAC alternating with IE, followed by radiation therapy, followed by consolidation chemotherapy with same regimen. About Twenty-one localized disease patients (25.3%) were treated by surgery followed by chemotherapy and radiation. Out of five patients with localized disease, who had undergone amputation, four had received adjuvant chemotherapy, and one did not receive any further treatment. Rest ten patients with metastatic disease at presentation were treated by palliative chemotherapy or radiotherapy or the combination of two.

Response to treatment

Table 2 demonstrates the response achieved by 72 patients with localized EWS postradical treatment with different treatment strategies.

At a median follow-up period of 16 months, out of 72 radically treated patients with localized disease at presentation, 37 (44.6%) patients failed the treatment. Majority of the failures (23 patients = 27.7%), out of 37, were distant. Four patients (4.8%) had both local and distant failure, and 10 (12%) failed locally. The most common site of distant failure was lung (18.1%), followed by bone (10.8%) and brain (4.8%) [Table 3].

For localized disease patients, the 1 year, 2 years, and 5 years DFS were 73.8%, 45.7%, and 33.2%, respectively. The median time to any failure was 11 months [Figure 1].

Table 1: Patients' profile and treatment details

Characteristics	Number of patients (%)
Gender	
Male	51 (61.4)
Female	32 (38.6)
Age (years)	
Median	18
Range	3-45
Metastasis at presentation	
Yes	11 (13.3)
No	72 (86.7)
Tumor site	
Extremity	44 (53)
Upper limb	15 (18.1)
Lower limb	29 (34.9)
Axial	9 (10.8)
Ribs/clavicle/scapula	15 (18.1)
Extraosseous	5 (6)
Skull	4 (4.8)
Pelvis	6 (7.2)
Tumor length (cm)	
>8	52 (62.7)
≤8	31 (37.3)
Treatment	
Surgery → CCT	4 (4.8)
Surgery → RT + CCT	21 (25.3)
CCT → RT → CCT	47 (55.6)
Surgery alone	1 (1.2)
Palliative CCT alone	6 (7.2)
Palliative RT + CCT	3 (3.6)
Palliative RT alone	1 (1.2)
Surgery type	
WLE	21 (80.7)
Amputation	5 (19.3)
Chemotherapy regimen	
VAC	46 (55.4)
VAC/IE	33 (39.8)
ICE	2 (2.4)

CCT: Chemotherapy, RT: Radiotherapy, WLE: Wide local excision, VAC: Vincristine, adriamycin, cyclophosphamide, IE: Ifosfamide-etoposide, ICE: Ifosfamide, cisplatin, and etoposide

Table 2: Response to treatment in localized Ewings sarcoma

	Complete response	Partial response	Progressive disease	Stable disease
Surgery alone	1			
Surgery → CCT	4			
Surgery → CCT → RT	17	1		2
Induction CCT → RT → CCT	29	4	3	6
CCT → RT	1	1	2	1

CCT: Chemotherapy, RT: Radiotherapy

Table 3: Pattern of failure

Failure type	Number of failures (%)
Total	37 (44.6)
Local	10 (12)
Distant	23 (27.7)
Lung	15
Bone	5
Brain	4
Local + distant	4 (4.8)
Bone	4

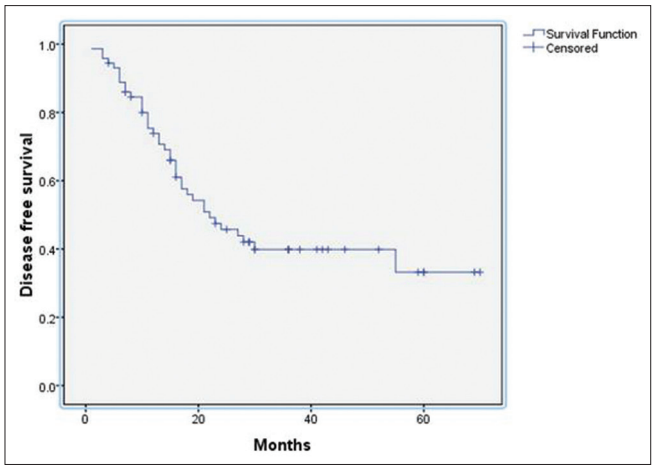

Figure 1: Disease-free survival

The 1 year, 2 years, and 5 years LCs were 73.3%, 65.1%, and 55.8%, respectively. The median time to local failure was 10 months [Figure 2].

Metastasis free survival

The 1 year, 2 years, and 5 years metastasis-free survival rates were 72.7%, 52.9%, and 45.3%, respectively. The median time to metastatic failure was 11.5 months.

Prognostic factors for local control and survival

By univariate analysis, the following features were found to be associated with a poor prognosis for local control: Axial site ($P < 0.03$), and chemotherapy regimen with VAC only ($P < 0.03$). Other factors however could not be proven to be significantly poor prognostic factors: Age older than 12 years ($P = 0.17$), sex ($P = 0.30$), disease length more than 8 cm ($P = 0.4$), fever ($P = 0.8$), anemia ($P = 0.5$), high serum lactate dehydrogenase (LDH) level ($P = 0.11$), and poor chemotherapy-induced necrosis ($P = 0.9$). By multivariate analysis, none of the factors were correlated to local control.

For survival, age >12 years ($P < 0.05$) was found to be the only factor associated with poor prognosis by both univariate and multivariate analysis. None of the other factors were found be to be prognostic for survival.

Attempt for salvage treatment

All recurrences were verified histologically, unless obvious by clinical examination or imaging. In patients with disease recurrence, salvage surgery, or palliative treatment with second-line chemotherapy and/or radiotherapy to painful metastatic sites was offered, depending on the status of the individual patient, their symptoms, and previous treatment.

Seven patients with lung metastasis were planned with chemotherapy by ICE regimen and showed only partial response to treatment. Other six patients were managed by supportive treatment only. All nine patients with bone metastasis had relapsed in vertebral level. They were started on steroids and planned with palliative radiotherapy to the spine to the dose of 30 Gy delivered in ten fractions in 2 weeks. Five patients out of these also received palliative chemotherapy with ICE. Four patients who relapsed in brain were given palliative radiotherapy to the brain and were managed by supportive care only. The median time to disease progression in these patients was 4 months.

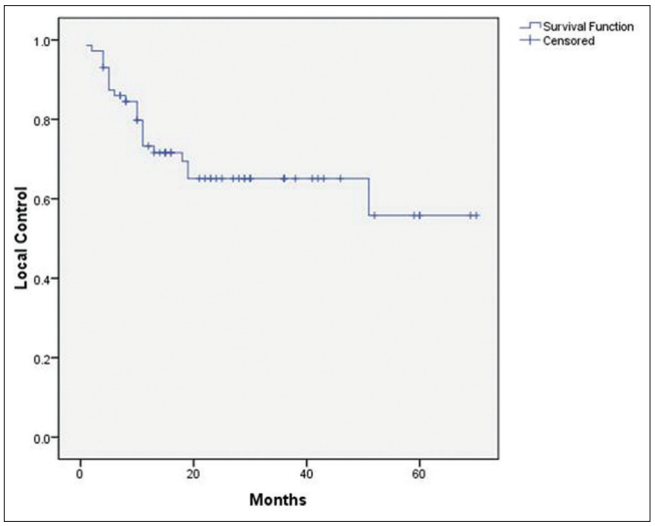

Figure 2: Local control rates

DISCUSSION

EWS is a small, blue, round cell bone tumor seen in the second decade of life.[7,13,14] In our study too, the median age was 18 years. Similar to the studies quoted in the literature,[15] the extremities were the most common site of presentation in our patients. The disease was found less common in axial region, extraosseous sites, chest wall, skull, and pelvic bones. Metastasis at presentation is often quoted to be seen in 25% patients, with lung being the most common site.[16-19] However, in our study, only 13% patients were metastatic though lung was still the most common site.

Metastatic disease at presentation, tumor volume more than 100 ml, axial location of tumor, and higher LDH levels are well-known poor prognostic factors for EWS.[20] However, only the metastatic disease at presentation has been proven to be of significant value in the literature.[21] In our study too, out of 11 patients (13%) who had metastasis at presentation, only one patient could complete the radical treatment and was disease free at the time of analysis. Rest all had progressive disease, and therefore, metastasis at presentation is clearly the poorest prognostic factor for survival.

Besides this, in our study, axial site ($P < 0.03$) and chemotherapy with VAC only regimen ($P < 0.03$)

were identified as prognostic factors for poor local control by univariate analysis. However, for survival, age >12 years ($P < 0.05$) was the only factor found to be poorly prognostic by both univariate and multivariate analysis. This may be due to more aggressive disease in adult patients compared to pediatric group, leading to their worse outcomes[22] although others have found no significant differences in survival.[23]

Other factors such as initial tumor volume or disease length,[20,24] serum LDH levels,[25] and necrosis after chemotherapy[26] did not correlate significantly as poor prognostic factors for local control and survival. One of the reasons could be that irrespective of the bulk of disease, different chemotherapy regimens have been used in these patients. This could have led to different necrotic rates in the tumor, and thereby producing bias in the results. The prospective randomized trials may be needed to prove these factors to be prognostic value.

Different treatment strategies are followed by different institutes in localized EWS. Chemotherapy is the common approach in almost all the strategies used nowadays. The difference lies in the choice of local therapy (surgery or radiation therapy) used. In our study, there was no survival difference between patients treated with surgery followed by adjuvant chemotherapy and those treated with neoadjuvant chemotherapy followed by local treatment and adjuvant chemotherapy. However, there was a definite survival difference between the patients who were treated by VAC alone and those treated by VAC alternating with IE, with survival advantage in the latter group ($P < 0.03$). Therefore, treatment plan can be optimized based on patient's disease status and institutional policy. Werier *et al*.[27] performed a systematic review to investigate the optimal treatment strategy among the options of surgery alone, radiotherapy alone, and the combination of radiotherapy plus surgery in the management of localized EWS of bone following neoadjuvant chemotherapy. When radiotherapy was compared with surgery, a meta-analysis combining two papers showed that surgery resulted in a higher event-free survival than radiotherapy in any location (hazard ratio [HR] =1.50, 95% confidence interval [95% CI] =1.12–2.00; $P = 0.007$). However, another paper did not find a statistically significant difference in patients with pelvic disease, and no papers identified a significant difference in overall survival. When surgery plus radiotherapy was compared with surgery alone, the meta-analysis did not demonstrate a statistically significant difference for event-free survival between the two groups (HR = 1.21, 95% CI = 0.90–1.63). Both surgical morbidities and radiation toxicities were reported. The study concluded that the optimal local treatment for an individual patient should be decided through consideration of patient characteristics, the potential benefit and harm of the treatment options, and patient preference.

In our study, 1 year, 2 years, and 5 years DFS were 73.8%, 45.7%, and 33.2%, respectively, which are lower than the 5 years survival results mentioned in the literature, ranging from 53% to 69%.[6-10,28,29] This can be explained by the fact that the studies mentioned above have included pediatric age group alone, which is a good prognostic factor for survival. However, in our study, approximately 75% patients had age more than 12. The LCs in our study were 73.3%, 65.1%, and 55.8% at 1 year, 2 years, and 5 years, respectively. This is however in accordance with the results in literature ranging from 53% to 93%.[30,31] Further patients treated with VAC alternating with IE had significantly better LCs than patients treated with VAC alone. Similar result has also been proven by INT-0091 trial, where 5 years local failure rates were 30% in VAC alone arm, compared to 11% only in VAC/IE arm.[32] Recently, Ben-Ami *et al*.[33] presented 15 years experience of treating patients of EWS with short aggressive course of chemotherapy (the MSKCC P6 protocol) and has shown that the outcome is comparable to that following other first-line treatment regimens in use (VAC alternating with IE), with potentially fewer long-term adverse events.

About 30–40% of patients experience recurrent disease either locally, distantly, or combined, and have a dismal prognosis.[30,34] In our study also, 37 patients (44.6%) patients failed, and on further treatment, they failed to achieve a fair progression-free survival.

CONCLUSIONS

Our study demonstrates that multimodality aggressive treatment approach for the localized EWS is significantly associated with improved control rates. Our analysis of the different treatment strategies brings about an important understanding that though EWS is considered a radio-chemosensitive tumor, still surgery should be offered as a part of treatment if the tumor is resectable. Furthermore, all patients with metastatic disease at presentation should be offered a radical treatment approach to achieve better progression-free survival rates.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Downing JR, Head DR, Parham DM, Douglass EC, Hulshof MG, Link MP, *et al*. Detection of the (11;22)(q24;q12) translocation

of Ewing's sarcoma and peripheral neuroectodermal tumor by reverse transcription polymerase chain reaction. Am J Pathol 1993;143:1294-300.
2. Subbiah V, Anderson P, Lazar AJ, Burdett E, Raymond K, Ludwig JA. Ewing's sarcoma: Standard and experimental treatment options. Curr Treat Options Oncol 2009;10:126-40.
3. Maheshwari AV, Cheng EY. Ewing sarcoma family of tumors. J Am Acad Orthop Surg 2010;18:94-107.
4. Bleyer A, O'Leary M, Barr R. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000. Bethesda, MD: National Cancer Institute; 2006.
5. Bacci G, Ferrari S, Bertoni F, Rimondini S, Longhi A, Bacchini P, *et al.* Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: Analysis of 359 patients at the Istituto Ortopedico Rizzoli. J Clin Oncol 2000;18:4-11.
6. Arndt CA, Crist WM. Common musculoskeletal tumors of childhood and adolescence. N Engl J Med 1999;341:342-52.
7. Jürgens H, Dirksen U. Ewing sarcoma treatment. Eur J Cancer 2011;47 Suppl 3:S366-7.
8. Barbieri E, Emiliani E, Zini G, Mancini A, Toni A, Frezza G, *et al.* Combined therapy of localized Ewing's sarcoma of bone: Analysis of results in 100 patients. Int J Radiat Oncol Biol Phys 1990;19:1165-70.
9. Yukhta TV, Punanov YA, Kazantsev IV, Malinin AP, Safonova SA, Gafton GI, *et al.* Combined therapy for children and adolescents with Ewing tumors (a 25-year experience). Vopr Onkol 2015;61:233-8.
10. Seker MM, Kos T, Ozdemir N, Seker A, Aksoy S, Uncu D, *et al.* Treatment and outcomes of Ewing sarcoma in Turkish adults: A single centre experience. Asian Pac J Cancer Prev 2014;15:327-30.
11. Rodríguez-Galindo C, Navid F, Liu T, Billups CA, Rao BN, Krasin MJ. Prognostic factors for local and distant control in Ewing sarcoma family of tumors. Ann Oncol 2008;19:814-20.
12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
13. Applebaum MA, Worch J, Matthay KK, Goldsby R, Neuhaus J, West DC, *et al.* Clinical features and outcomes in patients with extraskeletal Ewing sarcoma. Cancer 2011;117:3027-32.
14. Collier AB 3rd, Simpson L, Monteleone P. Cutaneous Ewing sarcoma: Report of 2 cases and literature review of presentation, treatment, and outcome of 76 other reported cases. J Pediatr Hematol Oncol 2011;33:631-4.
15. Franchi A. Epidemiology and classification of bone tumors. Clin Cases Miner Bone Metab 2012;9:92-5.
16. Esiashvili N, Goodman M, Marcus RB 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 2008;30:425-30.
17. Obata H, Ueda T, Kawai A, Ishii T, Ozaki T, Abe S, *et al.* Clinical outcome of patients with Ewing sarcoma family of tumors of bone in Japan: The Japanese Musculoskeletal Oncology Group cooperative study. Cancer 2007;109:767-75.
18. Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol 2010;11:184-92.
19. Ganjoo KN, Patel S. The treatment outcome for adult patients with Ewing's sarcoma. Curr Oncol Rep 2013;15:372-7.
20. Rodríguez-Galindo C, Liu T, Krasin MJ, Wu J, Billups CA, Daw NC, *et al.* Analysis of prognostic factors in Ewing sarcoma family of tumors: Review of St. Jude Children's Research Hospital studies. Cancer 2007;110:375-84.
21. Orr WS, Denbo JW, Billups CA, Wu J, Navid F, Rao BN, *et al.* Analysis of prognostic factors in extraosseous Ewing sarcoma family of tumors: Review of St. Jude Children's Research Hospital experience. Ann Surg Oncol 2012;19:3816-22.
22. Lee J, Hoang BH, Ziogas A, Zell JA. Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. Cancer 2010;116:1964-73.
23. Kaidar-Person O, Haim N, Bar-Sela G. Treatment of adult patients with Ewing's sarcoma: Compliance with chemotherapy protocols & toxicity. Med Oncol 2011;28 Suppl 1:S685-9.
24. Bacci G, Boriani S, Balladelli A, Barbieri E, Longhi A, Alberghini M, *et al.* Treatment of nonmetastatic Ewing's sarcoma family tumors of the spine and sacrum: The experience from a single institution. Eur Spine J 2009;18:1091-5.
25. Bacci G, Longhi A, Ferrari S, Mercuri M, Versari M, Bertoni F. Prognostic factors in non-metastatic Ewing's sarcoma tumor of bone: An analysis of 579 patients treated at a single institution with adjuvant or neoadjuvant chemotherapy between 1972 and 1998. Acta Oncol 2006;45:469-75.
26. Picci P, Böhling T, Bacci G, Ferrari S, Sangiorgi L, Mercuri M, *et al.* Chemotherapy-induced tumor necrosis as a prognostic factor in localized Ewing's sarcoma of the extremities. J Clin Oncol 1997;15:1553-9.
27. Werier J, Yao X, Caudrelier JM, Di Primio G, Ghert M, Gupta AA, *et al*. A systematic review of optimal treatment strategies for localized Ewing's sarcoma of bone after neo-adjuvant chemotherapy. Surg Oncol 2016;25:16-23.
28. Laurence V, Pierga JY, Barthier S, Babinet A, Alapetite C, Palangié T, *et al.* Long-term follow up of high-dose chemotherapy with autologous stem cell rescue in adults with Ewing tumor. Am J Clin Oncol 2005;28:301-9.
29. Smorenburg CH, van Groeningen CJ, Meijer OW, Visser M, Boven E. Ewing's sarcoma and primitive neuroectodermal tumour in adults: Single-centre experience in the Netherlands. Neth J Med 2007;65:132-6.
30. Bernstein M, Kovar H, Paulussen M, Randall RL, Schuck A, Teot LA, *et al.* Ewing's sarcoma family of tumors: Current management. Oncologist 2006;11:503-19.
31. Bedetti B, Wiebe K, Ranft A, Aebert H, Schmidt J, Jürgens H, *et al.* Local control in Ewing sarcoma of the chest wall: Results of the EURO-EWING 99 trial. Ann Surg Oncol 2015;22:2853-9.
32. Yock TI, Krailo M, Fryer CJ, Donaldson SS, Miser JS, Chen Z, *et al.* Local control in pelvic Ewing sarcoma: Analysis from INT-0091 – A report from the Children's Oncology Group. J Clin Oncol 2006;24:3838-43.
33. Ben-Ami T, Waldman E, Marc W, Weintraub M, Revel-Vilk S, Fried I. Ewing sarcoma: A 15-year experience of a single center with the MSKCC P6 treatment protocol. J Pediatr Hematol Oncol 2016;38:38-42.
34. Shankar AG, Pinkerton CR, Atra A, Ashley S, Lewis I, Spooner D, *et al.* Local therapy and other factors influencing site of relapse in patients with localised Ewing's sarcoma. United Kingdom Children's Cancer Study Group (UKCCSG). Eur J Cancer 1999;35:1698-704.