Archives of Clinical & Experimental Surgery

Original Article

Arch Clin Exp Surg 2017;6:195-200

doi:10.5455/aces.20161017105732

Are we able to predict the outcome of Ewing sarcoma? Looking for clinical prognostic factors by a multidisciplinary approach

Coral Sánchez Pérez[1], Lydia Mediavilla Santos[1], Esther Carbó Laso[1], Diana María Crego Vita[2], José Antonio Calvo Haro[1], Francisco Javier Vaquero Martín[1]

ABSTRACT

Objective: Our main goal was to assess the outcome of patients with Ewing sarcoma (EWS) and identify prognostic factors.
Methods: A retrospective review of 65 patients diagnosed with EWS at our institution between 1991 and 2013.
Results: Patients had a median age of 19 years (0.3-76), and 63.1% were males. Median tumor size was 10 cm (2-30). Primary sites included the limbs (42.2%), pelvis (23.4%), and chest wall (9.4%). 22 patients (34.4%) had metastatic disease. Treatment: Surgical resection in 45 patients (76.3%) and external beam radiotherapy in 48 patients (75%). Chemotherapy regimens: VAIA/EVAIA in 15 patients (33%), VAC/IE in 15 patients (33%), and VIAE in 10 patients (22%). After a mean follow-up of 40.7 months (p25-75; 13.3-86.16), 5-year actuarial overall survival (OS) and progression-free survival (PFS) were 67.34% and 49.2%, respectively. As determined by univariate analysis, OS was influenced by stage (p=0.0141) and chemotherapy (p= 0.036). Neither sex, age, LDH levels, primary tumor location, nor size, surgery, or radiation therapy were correlated to outcome. In the multivariate model, only stage remained significant (p<0.010).
Conclusion: Although no significant results were found, EWS outcomes are known to depend on many clinical and treatment variables. Further studies should include variables that possibly have prognostic value.

Key words: *Ewing sarcoma family of tumors, sarcoma surgery, chemotherapy, Ewing diagnosis*

Introduction

Ewing sarcoma was first described in 1920 by James Ewing as a diffuse endothelioma of bone and was labeled "Ewing sarcoma" in the tumor registry of the American College of Surgeons in 1921 [1].

Thanks to pathological, immunohistochemical, and cytogenetical advances, the Ewing sarcoma family of tumors (ESFT) may be defined as tumors of small round cells with a neuroectodermal origin and the same genetic translocation.

EWS is the second most common malignant bone tumor in people under 30, and is more frequent in white males [2].

Before multimodal therapy was introduced, five-year OS was 25%, while it presently reaches 70% (except if metastatic or recurrent disease occurs) [3-6].

Factors known to affect disease outcomes include age, tumor size, tumor site, metastases, and histological response to chemotherapy [7]. However, because of the non-specific clinical signs and high variability in

Author affiliations : *Department of Orthopaedic Surgery, [1]Hospital General Universitario Gregorio Marañón, Spain [2]Hospital Central de la Defensa Gomez Ulla, Madrid, Spain*
Correspondence : *Coral Sánchez Pérez, MD, Hospital General Universitario Gregorio Marañón, Madrid, Spain. e-mail: spcoral@gmail.com*
Received / Accepted : *August 11, 2016 / August 24, 2016*

treatment response, research is ongoing on the diagnostic and prognostic factors of EWS [8].

Materials and Methods

An observational, retrospective study was conducted of 65 patients diagnosed with EWS at our institution from 1991 and 2013.

Demographic and clinical information was collected from the clinical histories of the patients.

Sex, age, tumor size (largest tumor diameter), primary tumor site, stage at diagnosis (with or without metastasis), lactate dehydrogenase (LDH) levels at diagnosis, local treatment received (surgery, radiation therapy), systemic treatment (chemotherapy protocol), and clinical outcome were recorded.

Clinical features recorded included disease stage and Eastern Cooperative Oncology Group (ECOG) performance status scale after treatment. Disease stage was classified as complete remission, partial remission, stable disease, and progressive disease. Complete remission was defined as no tumor mass, partial remission with at least a 30% reduction in largest tumor diameter, progressive disease as 20% tumor growth or a new mass, and stable disease in all other cases.

Statistical Analysis

Descriptive analysis was performed of the clinical and demographic variables.

Continuous variables are given as mean and standard deviation, while categorical variables are given as percentages. Non-normally distributed numerical variables are presented as median and interquartile range (p25; p75). Patient survival and time to event periods are described by Kaplan-Meier curves and log-rank tests to compare survival distributions. Cox regression was used to calculate hazard ratios for survival and progression.

Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 21.0 (IBM Corp. Armonk, NY) was utilized for the statistical analysis. Values of $p < 0.05$ were considered statistically significant.

Results

Descriptive analysis

Our sample consisted of 65 patients, 41 being male (63.1%), with a mean age at diagnosis of 19 years (0.2-76).

The mean largest tumor size was 10 cm (2-30), and 70% of tumors were larger than 8 cm. The mean cell proliferation index, ki67, was 53.6% (10-90). The most common primary tumor sites included the limbs (42.2%), pelvis and lumbosacral region (23,4%), chest wall (9,4%), kidney, colon and abdomen (6.3%), skull and maxillofacial bones (4.7%), retroperitoneal and paravertebral space (3.1%), and brain (11%). 22 patients (34.4%) had metastases at diagnosis and 42 (65.6%) localized disease. LDH at diagnosis was elevated in 48.6% patients. ECOG performance status was ECOG 0 in 67.3%, ECOG 1 and 2 in 28.8%, and ECOG 3 and ECOG 4 in none.

Treatment protocols: Vincristine, doxorubicin (Adriamycin®) cyclophosphamide, ifosfamide, etoposide (VAC/IE) in 33.3%, VAIA/EVAIA in 33.3%, VIAE in 22.2%, and others 11%. 48 patients received radiation therapy (75%) and 45 patients underwent surgery (76.3%). Patients were followed up for a mean of 40.7 months (p25-75; 13.3-86.16). Five-year OS and PFS were 67.34% and 49.2%, respectively. Mean OS was 156.53 months (95% confidence interval (CI) 121-192) and median PFS 49.83 months (95% CI 20-168).

Recurrence or progression was found in 36 patients (55.4%). Median time to recurrence was 6.8 years (Figure 1).

After treatment, 60% of patients achieved complete

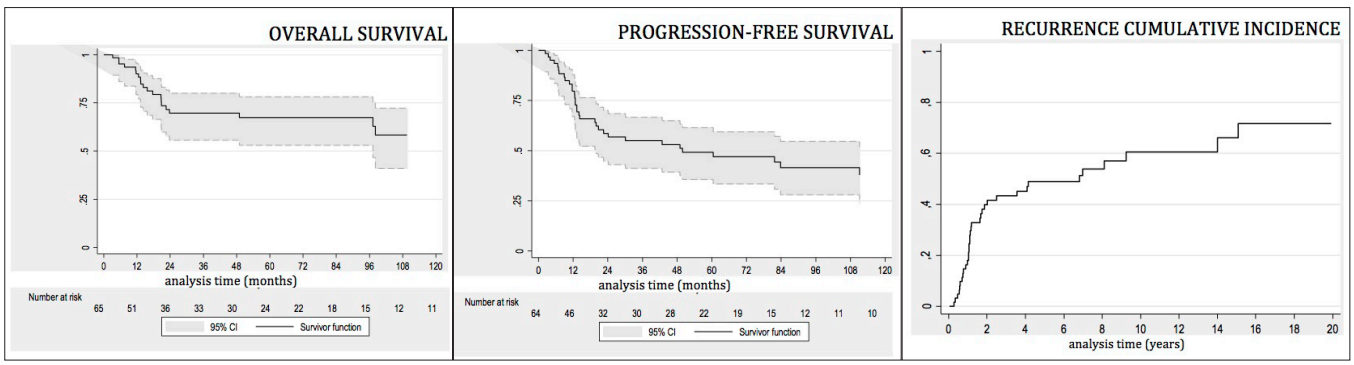

Figure 1. OS, PFS, and recurrence.

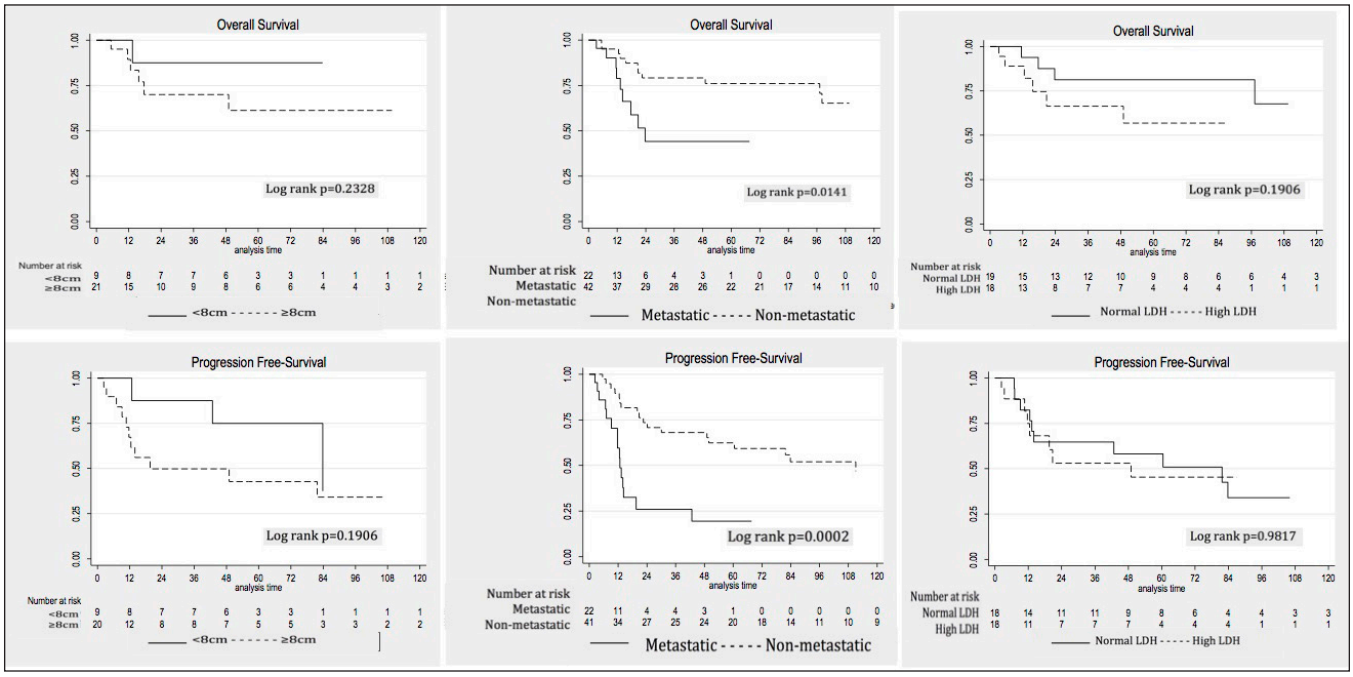

Figure 2. Univariate analysis of five-year OS and PFS in patients with tumoral sizes larger and smaller than 8cm, patients with or without metastasis at diagnosis, and patients with high and normal levels of LDH at diagnosis.

remission, 13.3% partial remission, and 2.2% stable disease, while 24.4% had progressive disease. When last seen (2015), 43% of patients were alive, 37% had died, and 20% were lost during follow-up.

Univariate analysis

Five-year PFS was 19.5% in patients with metastasis at diagnosis and 62.4% in patients with localized disease (p=0.0002, hazard ratio (HR) 0.26). The progression rate was 62% when tumor size was greater than 8 cm and 33% when tumor size was less than 8 cm (p=0.15). PFS was 75% when tumor size was smaller than 8 cm and 42.72% when tumor size was larger than 8 cm (p=0.19). Recurrence or progression risk increased 6.9% (95% CI 0.1-14) with each 1-cm increase in tumor size. Patients treated with surgery had a lower progression rate (51%) than those that did not undergo surgery (64%) (p=0.39). They also had higher PFS rates (57% vs 31%; p=0.165, HR 0.58).

Five-year OS was 44% in patients with metastasis at diagnosis compared to 76% in those with localized disease (p=0.0141, HR=0.32). Patients with tumors larger and less than 8 cm had five-year OS rates of 61.3% and 87.5%, respectively (p=0.23). The OS rate in patients that had surgery was 72% versus 59.6% in those that did not (p=0.755). With regards to chemotherapeutic treatments, less progression was seen in patients treated with VAC/IE or VAIA/EVAIA protocols (Pearson's correlation of 0.02). Although the groups of patients treated with VAC/IE or VAIA/EVAIA had the highest number of survivors, the difference in OS was not statistically significant (p=0.19). An analysis of response to chemotherapy yielded no statistical difference between metastatic and localized disease. Greater progression and recurrence rates were seen when the pelvic or chest wall were involved (p=0.557). In patients with high baseline LDH levels, five-year OS was 57% and five-year PFS 45.4% compared to 81% and 58%, respectively, in patients with normal LDH levels at diagnosis.

Sex, age, local radiation therapy, and primary tumor site were factors independent from OS and PFS (Figure 2).

Multivariate analysis

With the multivariate analysis, only the presence or absence of metastasis at diagnosis remained a risk factor for PFS decrease (Figure 3, Table 1).

Discussion

Metastasis, primary tumor site, tumor size, age, response to chemotherapy, surgery and radiation therapy, and high LDH levels at diagnosis have already been investigated as possible prognostic factors for the ESFT. However, no adequate evidence exists in the literature with respect to metastatic disease at diagnosis, tumor size, and response to chemotherapy.

Table 1. Multivariate analysis of recurrence or progression and primary tumoral site.

Recurrence/Progression	Limbs	Pelvis, lumbosacral	Chest wall	Others	Total
NO	13	5	2	9	29
	48.15	33.3	33.3	45.31	45.31
YES	14	10	4	7	35
	51.85	66.67	66.67	43.75	54.69
Total	27	15	6	16	64
	100	100	100	100	100

Pearson $Chi^2(3) = 2.0761$, $Pr = 0.557$

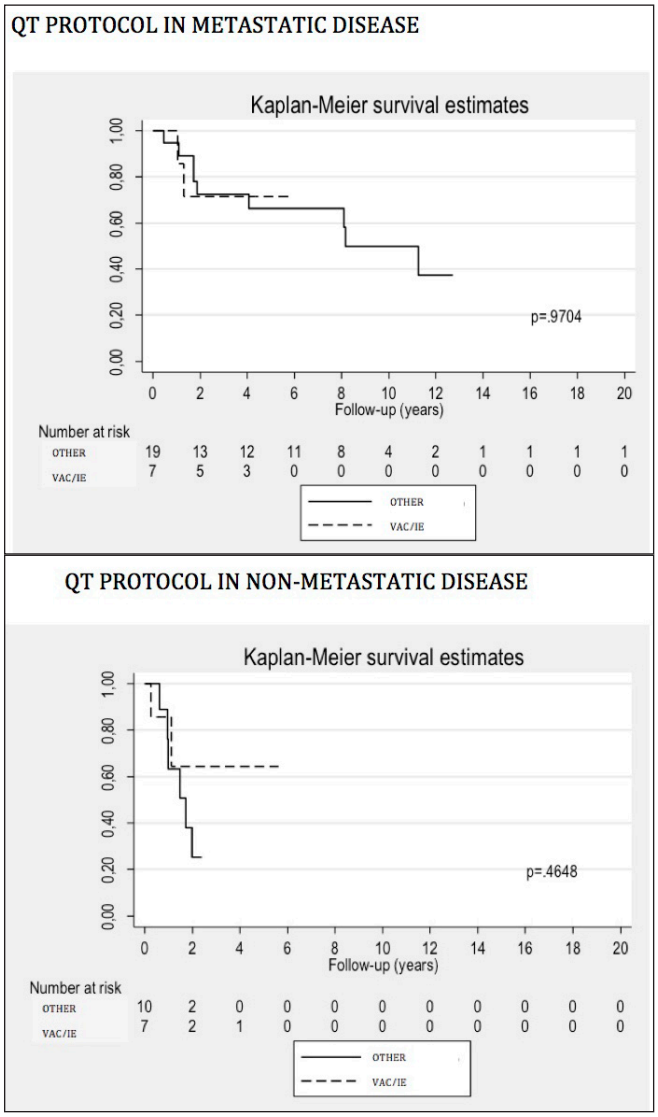

Figure 3. Multivariate analysis of OS and PFS in patients with or without metastatic disease at diagnosis, treated with different chemotherapy protocols (VAC/IE vs other protocol).

In our cohort, metastatic disease was found in 34.4% of patients who had five-year OS and PFS rates of 44% and 19.5%, respectively. Our results are similar to those reported over the last 15 years (OS rates ranging from 34%-38%) [7,9,10].

When response to chemotherapy was investigated in patients with or without metastasis at diagnosis, a major difference was seen between losses in patients without metastatic disease treated with VAC/IE and those treated with a different protocol (28.6% vs 80% patients lost, p=0.464). This difference was not found in the metastatic disease group (31.6% vs 29%, p=0.97). Although statistical significance was not reached, this major disparity in response to chemotherapy between patients with and without metastasis supports the approach of certain studies that have attempted to create different risk groups to adapt chemotherapy protocols [11-16].

Primary tumor sites have been established as the second most important variable in ESFT prognosis. The pelvic region and axial skeleton are the locations with the worst prognoses [8,9,17]. The data from our study are comparable to that already described in the literature.

Tumor size continues to be a controversial subject. Various studies have not been able to find an independent relationship between tumor size and survival [18], while others consider tumor size as a risk factor when associated with specific laboratory and clinical conditions [13], and still other studies consider it to be an independent risk factor [9,14,17,19]. Our analysis demonstrated no statistical significance for OS or PFS, but a relationship was determined between recurrence or progression for each 1-cm increase in tumor size (HR= 1.069). If we potentially increased our sample size, we may have acquired a significant value.

High LDH levels at diagnosis are a proven risk factor [8,11,12,20]. Results from the present work agree with those already reported. OS decreases when high LDH levels are measured at diagnosis.

Surgery increases PFS and OS with or without ra-

diation therapy [11,16,17,21]. We showed great differences in OS within our study, though statistical significance was not reached. Group heterogeneity and small sample size may account for these findings. Tumors with easier surgical access or with or without necrosis from resected specimens were found to be a factor that is prognostic for disease outcomes in a number of studies [14,18,20], and they were not controlled either.

Radiation therapy is currently used as adjuvant therapy for surgery and in the case of recurrence, unresectable tumor, non-safe margin resection, or limb-sparing surgery [8,22]. The lack of randomized trials makes it difficult to know the actual role of radiation therapy. No relationship was observed in our study between radiation therapy and survival [17]. As the current studies are not randomized, there is no standard treatment guideline, and they are affected by treatment selection bias (age, tumor site and size, or presence of metastasis). In recent years, new radiation therapy technologies have allowed groups to administer extended radiation therapy to overcome this treatment bias [23-26].

Conclusion

Metastatic disease, tumor size, tumor site, and high LDH levels at diagnosis are prognostic factors for ESFT outcomes.

No statistical significance was found for chemotherapy protocols or surgery in our cohort, probably because of study limitations, including small sample size, group heterogeneity, and retrospective analysis.

Great effort has already been exerted to learn how to detect demographic and clinical factors that will allow selecting different treatment options. Future studies controlling for demographic factors (race, sex, age), clinical factors (time since onset, presence or absence of metastasis at diagnosis, tumor site, tumor size, LDH and erithrocyte sedimentation rate (ESR) levels, complete blood count, pathological examination, ki67 index), therapeutic factors (chemotherapy protocols and toxicity, surgical procedure, safety margins, necrosis, radiation therapy, and toxicity), and outcome factors (quality of life, survival, disease progression) are needed to understand ESFT.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Ewing J. Diffuse Endothelioma of Bone. Proc New York Pathol Soc 1921;21:17-24.
2. Heck RK,Toy PC. Malignant tumors of bone. In: Azar FM, Beaty JH, Canale ST (eds.) Campbell's Operative Orthopaedics Twelfth edition. Elsevier, Philadelphia;918-20.
3. Jaffe N, Paed D, Traggis D, Salian S, Cassady JR. Improved outlook for Ewing's sarcoma with combination chemotherapy (vincristine, actinomycin D and cyclophosphamide) and radiation therapy. Cancer 1976;38(Table 1):1925-30.
4. Karski EE, McIlvaine E, Segal MR, Krailo M, Grier HE, Granowetter L, et al. Identification of Discrete Prognostic Groups in Ewing Sarcoma. Pediatr Blood Cancer 2016;63:47-53.
5. Yoon JH, Kwon MM, Park HJ, Park SY, Lim KY, Joo J, Park BK. A study of docetaxel and irinotecan in children and young adults with recurrent or refractory Ewing sarcoma family of tumors. BMC Cancer 2014;14:622.
6. Jiang Y, Ludwig J, Janku F. Targeted therapies for advanced Ewing sarcoma family of tumors. Cancer Treat Rev 2015;41:391-400.
7. 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.
8. Calvo JA, Álvarez RM, Cuervo M. Sarcoma de Ewing. In: Aboulafia A, Ramos LR (eds) [Tumores Óseos Malignos, Monografía][Article in Spanish]. SECOT publishing, Madrid, 2014;37-48.
9. Duchman KR, Gao Y, Miller BJ. Prognostic factors for survival in patients with Ewing's sarcoma using the surveillance, epidemiology, and end results (SEER) program database. Cancer Epidemiol 2015;39:189-95.
10. Paulussen M, Ahrens S, Burdach S, Craft A, Dockhorn-Dworniczak B, Dunst J, et al. Primary metastatic (stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies. European Intergroup Cooperative Ewing Sarcoma Studies. Ann Oncol 1998;9:275-81.
11. 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 (Madr) 2006;45:469-75.
12. Bacci G, Ferrari S, Bertoni F, Rimondini S, Longhi A, Bacchini P, et al. Prognostic factors in non-metastatic Ewing ' s sarcoma of bone treated with adjuvant chemotherapy : analysis of 359 patients at the Instituto Ortopedico Rizzoli. J Clin Oncol 2000;18:4-11.
13. Biswas B, Rastogi S, Khan SA, Shukla NK, Deo SV, Agarwala S, et al. Developing a prognostic model for localized Ewing sarcoma family of tumors: A single institutional experience of 224 cases treated with uniform chemotherapy protocol. J Surg Oncol 2015;111:683-9.
14. Oksüz DC, Tural D, Dincbas FÖ, Dervisoglu S, Turna H, Hiz M, et al. Non-metastatic Ewing's sarcoma family of tumors of bone in adolescents and adults: prognostic factors and clinical outcome-single institution results. Tumori 2014;100:452-8.
15. Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, et al. 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 2012;30:4148-54.
16. Ladenstein R, Potschger U, Le Deley MC, Whelan J, Paulussen M, Oberlin O, et al. Primary Disseminated Multifocal Ewing Sarcoma: Results of the Euro-EWING 99 Trial. J Clin Oncol 2010;28: 3284-91.
17. Lee J, Hoang BH, Ziogas A, Zell J. Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. Cancer 2010;116:1964-73.
18. Pan HY, Morani A, Wang WL, Hess KR, Paulino AC, Ludwig JA, et al. Prognostic Factors and Patterns of Relapse in Ewing Sarcoma Patients Treated With Chemotherapy and R0 Resection. Int J Radiat Oncol 2015;92:349-57.
19. Jürgens H, Göbel V, Michaelis J, Ramach W, Ritter J, Sauer R, et al. [The Cooperative Ewing Sarcoma Study CESS 81 of the German Pediatric Oncology Society--analysis after 4 years][Article in German]. Klin Padiatr 1985;197:225-32.
20. Marino MT, Grilli A, Baricordi C, Manara MC, Ventura S, Pinca RS, et al. Prognostic significance of miR-34a in Ewing sarcoma is associated with cyclin D1 and ki-67 expression. Ann Oncol 2014;25:2080-6.
21. Cotterill SJ, Ahrens S, Paulussen M, Jürgens HF, Voûte PA, Gadner H, et al. Prognostic factors in Ewing's tumor of bone: Analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol 2000;18:3108-14.
22. PDQ® Pediatric Treatment Editorial Board. PDQ Ewing Sarcoma Treatment. Bethesda, MD: National Cancer Institute. Updated September 28, 2016, Available at: http://www.cancer.gov/types/bone/hp/ewing-treatment-pdq. Accessed August 24, 2016 [PMID: 26389480].
23. 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)][Article in Russian]. Vopr Onkol 2015;61:233-8.
24. Sole CV, Calvo FA, Polo A, Cambeiro M, Gonzalez C, Desco M, et al. Intraoperative Electron-Beam Radiation Therapy for Pediatric Ewing Sarcomas and Rhabdomyosarcomas: Long-Term Outcomes. Int J Radiat Oncol Biol Phys 2015;92:1069-76.
25. Donaldson SS. Ewing sarcoma: radiation dose and target volume. Pediatr Blood Cancer 2004;42:471-6.
26. McGovern SL, Mahajan A. Progress in radiotherapy for pediatric sarcomas. Curr Oncol Rep 2012;14:320-6.