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Knowing about Ewing Sarcoma

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Review Article

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Abstract

Ewing's sarcoma is a malignant small, round, blue cell tumour[1]. It is a rare disease in which cancer cells are found in the bone or in soft tissue[1]. The most common areas in which it occurs are the pelvis, the femur, the humerus, the ribs and clavicle (collar bone)[1]. Ewing Sarcoma is the second most common primary bone sarcoma with 900 new diagnoses per year in Europe (EU27) [2] . Ewing's sarcoma in the United States is most common in the second decade of life, with a rate of 0.3 cases per million in children under 3 years of age, and as high as 4.6 cases per million in adolescents aged 15–19 years [3]. Whereas cases very rarely occurringin African or Asian populations [11,12,13,14]. Internationally the annual incidence rate averages less than 2 cases per million children.[4]

Keywords: *Sarcoma, Ewing disease, disease management.*

Introduction

Ewing sarcoma is the second most common primary bone sarcoma[2]. It is an orphan state disease with approximately 900 new diagnoses a year in Europe[2,5] . It is also called the Ewing Sarcoma Family of Tumours (ESFT) and includes Ewing sarcoma of bone, extra-osseous Ewing sarcoma, Primitive Neuroectodermal (PNET) and Askin's tumours[2]. Ewing sarcoma is diagnostically defined by a Ewing sarcoma EWS (chromosome 22) translocation resulting in fusion with an ETS transcription factor, the commonest abnormality (85%) being EWS-FLI1 (chromosome 11)[2]. Ewing sarcoma is a disease affecting children and young adults with a peak incidence at age fifteen[2]. It represents approximately 1% of all cancers reported in children but approximately 30% of all bone tumors in them [6,7,8]. The frequency of Ewing sarcoma in the population younger than 20 years old is approximately 2.9 per million [9].

RISK FACTORS OF EWING SARCOMA

Genetic

Chromosomal translocations involving transcription factor genes have been identified in an increasingly wide range of cancers [15]. Some translocations can create a protein "chimera" that is composed of parts from different proteins [15]. How such chimeras cause cancer, and why they cause cancer in some cell types but not others, is not understood [15]. One such chimera is EWS-FLI, the most frequently occurring translocation in Ewing Sarcoma, a malignant bone and soft tissue tumor of children and young adults [15]. They are characterized by chromosomal translocations leading to the generation of fusion proteins between EWS (or very rarely FUS) and members of the E-twenty-six (ETS) family of transcription factors that are capable of transforming cells. EWS/FLI1, the most frequent fusion, is thought to cause transformation through activation or repression of specific target genes [16].

Age

The median age at diagnosis was 10 years old (range, 2-17) and the median follow-up for survivors 8.6 years (range, 1-18.8) [17]. Thirty-two relapses occurred (21 distant, 5 local and 6 both). The 2- and 5-year overall survival rates were 70% and 51%, respectively [17]. Multivariate analysis showed four significant independent predictors for death: age ≥14 years old (HR: 5.06; p=0.019), lack of complete response (HR: 8.04; p<0.001), tumour volume≥150 ml (HR: 2.21; p=0.045) and distant recurrences (HR: 1.45; p=0.001) [17]. The other researched found 27% <18 years, 21% >40 years and 1-272 months follow-up (median 41). Age was significantly associated with overall survival (OS) (p = 0.01), whereby <18 years had a higher probability of 5-year survival (OS 61%) than >40 years (OS 37.6%) [20].

Race

Among 135 patients, 127 (19 Hispanic and 108 white/non-Hispanic) were analyzed (excluding small sample sized groups) finding 15% Hispanic, 85% non-Hispanic [20]. Ethnicity was marginally statistically significant (OS, p = 0.065); whereby median survival was clinically significant (white non-Hispanic 63 months and Hispanic 23 months) [20]. Hispanic ethnicity and older age are independent poor prognostic factors [20].

Ewing Sarcoma is almost exclusively a disease of white children [31,32,33]. Rates in whites are approximately 9 times those in blacks [31,32,33].

SIGN AND SYMPTOMS EWING SARCOMA

Pain that is more severe at night than during the day is generally accepted as a typical symptom of a primary malignant bone tumor[30]. Letson et al.[26] stated: "In contrast, pain from a musculoskeletal malignancy is often continuous and dull [30]. It is usually severe at rest and is characteristically worse at night [30]." Simon and Finn [27] stated that "unremitting pain or pain that is more severe at rest or at night than during the day is often considered as a symptom of a malignant disease[30]." The present study showed that pain at night was not a dominant initial symptom of malignant bone tumors as only twenty-one (21 percent) of the osteosarcomas and nine (19 percent) of the Ewing sarcomas caused pain at night[30]. However, pain related to strain and intermittent pain at rest were frequent; as these symptoms are also common in several benign musculoskeletal disorders, they can easily lead to an inaccurate diagnosis. Consistent with previous studies [28,29,30], fourteen (30 percent) of the patients with Ewing sarcoma had unexplained periods of fever [30].

Pain is the most common symptom of bone cancer[1]. Symptoms may vary depending on the position in the body and the size of the cancer[1]. There may be some swelling in the affected area and it may become tender to touch[1]. Bone cancer is sometimes discovered when a bone that has been weakened by cancer breaks after the child has a minor fall or accident[1].

TREATMENTS EWING SARCOMA

The median age of 27 patients was 24 years (range, 16-54 years) [18]. The median follow-up was 31.8 months (range, 6-144 months) [18]. Tumor size was between 1.5 and 14 cm (median: 8 cm) [18]. Eighty-five percent of patients had localized disease at presentation and 15% had metastatic disease [18]. Local therapy was surgery alone in 16% of patients, surgery combined with radiotherapy in 42% and radiotherapy alone in 27%. All patients were treated with vincristine, doxorubicin, cyclophosphamide and actinomycin-D, alternating with ifosfamide and etoposide every 3 weeks. In patients with localized disease at presentation, the 5-year event-free survival and overall survival were 59.7 and 64.5%, respectively [18]. At univariate analysis, patients with tumor size≥ 8 cm, high serum lactate dehydrogenase, metastasis at presentation, poor histological response to chemotherapy and positive surgical margin had significantly worse event-free survival [18]. The significant predictors of worse overall survival at univariate analysis were tumor size≥8 cm, high lactate dehydrogenase, metastasis at presentation, poor histological response to chemotherapy, radiotherapy only as local treatment and positive surgical margin [18].

Huang studies have found from seven male and five female patients and their mean age at diagnosis was 22 years (range, 12-48 years) [19]. Two patients (16.7%) had distant metastasis at diagnosis [19]. The primary tumor sites were the trunk in seven patients (58.3%) and the extremities in five patients (41.7%) [19]. Eleven patients received neoadjuvant chemotherapy followed by wide excision surgery, and then adjuvant chemotherapy [19]. One patient received only chemotherapy without surgical intervention due to poor cardiac and pulmonary function [19]. At a mean follow-up of 33 months, the 2-year overall survival rate (OS) was 45.5% [19]. Distant metastasis was the only statistically significant prognostic factor of OS in this study [19]. The 2-year OS rates of patients with lung metastasis and without lung metastasis were 0% and 42.9%, respectively (p = 0.021). The t(11;22)(q24:q12) translocation was present in all patients in our series [19].

Parida studies have found three patients had distant metastatic disease at diagnosis (lung [n = 2]; ipsilateral axillary lymph node[(n = 1]) [21]. All patients had painful swelling at the primary site, and 2 (22%) had pathological fracture [21]. All patients received chemotherapy and local control measures (surgery [n = 6], radiation [n = 2], surgery and radiation [(n = 1]). Three patients received radiotherapy for distant metastases [21]. Three patients had systemic recurrence (lungs [n = 2], lung and brain [n = 1]); none had local tumor recurrence [21]. Median follow-up was 5 years. Five patients (55.6%) are alive at last follow-up [21].

Mora studies have found twenty-four patients had loco-regional disease and seven had metastases [23]. The 4-year event-free survival (EFS) rate for patients with localized tumors is 83% and overall survival (OS) is 92% [23]. The 3-year EFS rate for patients with distant metastases is 28% and OS rate is 42% [23]. EWS-FLI1 fusion genes were detected in 17 cases (74%) and EWS-ERG in six cases (26%) [23]. Type 1 EWS-FLI1 variant was present in 6/7 metastatic patients and 3/16 loco-regional cases (P = 0.001) [23]. None of the patients experienced tumor progression before remission [23]. All relapses occurred within 2 years from the end of treatment and local relapses (n = 3) happened in patients who did not receive radiation therapy [23]. No secondary malignancies

have been observed, median follow-up of 4.3 years for surviving patients [23].

Table 1. Chemotherapy Protocol for Ewing Sarcoma[25]

REA-2: Adjuvant protocol
([VC/AD] [VC/CP]) two times ([VC/AC] [VC/AD] [VC/CP]) six times
Vincristine 1.4 mg/m2 IV push (2 mg max)
Doxorubicin 20 mg/m2 IV over 4 h/d 3 3 days
Cyclophosphamide 500 mg/m2 IV over 30 min/d 3 2 days
Dactinomycin 15 mg/kg/d IV push (2 mg max) 3 4 days
REN-1: Neoadjuvant protocol
Induction: ([VC/CP/AD]) three times
Maintenance: ([VC/CP] [AD] [AC]) six times (no AD in the last cycle)
Vincristine 1.5 mg/m2 IV push (2 mg max)
Doxorubicin 20 mg/m2 IV over 4 h/d 3 3 days
Cyclophosphamide 1200 mg/m2 IV over 30 minutes
Dactinomycin 0.5 mg/m2 IV push/d 3 3 days (2 mg max)
REN-2: Neoadjuvant protocol
Induction: ([VC/CP/AD]) two times
Maintenance: ([VC/CP/AD] [VC/IF/AC]) three times ([ET/IF] [VC/CP/ AC]) two times
Vincristine 1.5 mg/m2 IV push (2 mg max)
Doxorubicin 40 mg/m2 IV over 4 h/d 3 2 days
Cyclophosphamide 1200 mg/m2 IV over 30 minutes
Ifosfamide 1.8 mg/m2 IV over 1 h/d 3 5 days
Dactinomycin 1.25 mg/m2 IV push (2 mg max)
Etoposide 100 mg/m2 IV over 1 hour 3 5 days
REN-3: Neoadjuvant protocol
Induction: ([VC/CP/AD] [VC/IF/AC] [VC/CP/AD])
Maintenance: ([VC/CP/AD] [VC/IF/AC]) two times ([VC/CP/AC]) ([ET/ IF] [VC/CP/AD]) two times ([ET/IF])
Vincristine 1.5 mg/m2 IV push (2 mg max)
Doxorubicin 40 mg/m2 IV over 4 h/d 3 2 days
Cyclophosphamide 1200 mg/m2 IV over 30 minutes
Ifosfamide 1.8 mg/m2 IV over 1 h/d 3 5 days
Dactinomycin 1.25 mg/m2 IV push (2 mg max)
Etoposide 100 mg/m2 IV over 1 hour 3 5 days

Abbreviations: VC, vincristine; IV, intravenously, max, maximum; AD, doxorubicin; CP, cyclophosphamide; AC, dactinomycin; IF, ifosfamide; ET, etoposide.

Radiotherapy

Radiation therapy is most often used as first-line curative therapy [37]. ES is extremely radiosensitive and can be cured with relatively low doses of radiation, if metastasis has not occurred [36,37]. Radiation is often used preoperatively to reduce tumor size prior to surgical removal [37].

Chemotherapy

Chemotherapeutic drugs are most effective against fast-growing malignant cells [37]. Some drugs work during a specific cell cycle (cell-cycle specific) [37]. Others work during all phases of the cell cycle (cell-cycle non-specific) [37]. Chemotherapeutic agents are combined to produce the largest tumor kill with the least amount of normal-cell damage [37,38]. The use of cell-cycle specific agents (vincristine and 5-FU) and cell-cycle non-specific agents (cyclophosphamide and Adriamycin) are examples of combinations that provide this benefit[37,38]. Recent research findings indicate that alternating chemotherapy agents can be very effective in the treatment of ES [37,38].

The response to chemotherapy was evaluated by tumor necrosis, graded according to the modified criteria of Rosen et al. [39,40] In brief, 100% tumor necrosis is classed as grade 3; <10% viable tumor is grade 2; from 10% to 50% viable tumor is grade 1; and from 50% to 100% viable tumor is grade 0 [39,40].

Surgery

Surgery is the oldest recorded form of curative treatment for cancer [37]. Surgery is used in the ES patient for diagnosis, treatment (primary, adjuvant, salvage, and pallative), second-look procedures, and reconstruction [37]. Primary surgery was the preferred treatment for many years; removing both the tumor and large areas around the tumor site often resulted in amputation [37]. Today, advances in limb-saving surgical techniques (an adjuvant surgery) mean that many patients do not need amputation [37]. The tumor site and surrounding bone is removed and donor bone is grafted to replace diseased bone [37].

SIDE EFFECTS OF TREATMENTS EWING SARCOMA

Olmos studies have found 29 patients, 16 of whom had Ewing's sarcoma, were enrolled and received a total of 177 cycles of treatment (median 2, mean 6.1, range 1-24) [24]. Grade 3 deep venous thrombosis, grade 3 back pain, and grade 3 vomiting were each noted once in individual patients; one patient had grade 3 increases in aspartate aminotransferase and gammaglutamyltransferase concentrations [24]. This patient also had grade 4 increases in alanine aminotransferase concentrations [24]. The only other grade 4 adverse event was raised concentrations of uric acid, noted in one patient [24]. Pharmacokinetics were comparable between patients with sarcoma and those with other solid tumours [24]. 28 patients were assessed for response; two patients, both with Ewing's sarcoma, had objective responses (one complete response and one partial response) and eight patients had disease stabilisation (six with Ewing's sarcoma, one with synovial sarcoma, and one with fibrosarcoma) lasting 4 months or longer [24].

Patients receiving cancer therapy usually will have an effect that is myelosuppresive which chemotherapy drugs will cause bone marrow

suppression which results in red blood cells, white blood cells and plateles[25].

The use of drugs should be considered highly Metorexhate side effects on the kidney (nephrophaty) [24].

CLINICAL OUTCOMES EWING SARCOMA

Ten of the 19 patients who were operated on are alive. All those patients that were not operated on have died [22]. The length of survival in the whole group has ranged from 8 months to 8.5 years (mean 2.8 years) [22]. Mean overall survival among these patients that were operated on is 3.1 years, and among those who had lung metastases at baseline and underwent metastatectomy, the survival rate is 4.3 years [22]. The average survival rate among the non-operated on patients is 1.6 years [22].

The median of the follow-up survival time was 33 months (range, 9e84 months) [39]. Of the twelve patients, six (50%) died of the disease, and the remaining six patients were disease-free at the time of the last follow-up [39]. The 2-year and 3-year overall survival (OS) rates were 45.5% and 22.7%, respectively [39]. The 2- year OS of the patients without metastasis was 100%, while that of patients with metastasis was only 16.7% (p¼0.014) [39]. In addition to the two patients with distant metastases at diagnosis, four patients (40.0%) developed distant metastases within a mean follow-up period of 19 months [39]. Of the six patients with distant metastases, three had metastases to the lungs, two to the vertebral bodies, and one patient had metastases to both locations. Interestingly, the 2-year OS rates of the patients with lung metastasis and those without lung metastasis were 0% and 42.9%, respectively (p ¼ 0.021) [39]. The 2-year OS rates of patients with and without distant bone metastases were not significantly different (p ¼ 0.103) [39].

Conclusion

Ewing sarcoma is a type of bone cancer that usually occurs in children younger than 18 years old. Ewing sarcoma usually occurs in the white race. Genetic factors are still a factor cause's cancer in general. Signs and symptoms of Ewing sarcoma is a pain in a certain part of the bone and may have swelling of the section. For cancer that has not experienced metastases usually done for cancer surgery whereas happened metastases are usually given chemotherapy and radiotherapy. Side effects of treatment of Ewing sarcoma is myelosuppresive, this happens in cancer treatment using chemotherapy. Besides the side effects of chemotherapy itself such as nausea, vomiting and impaired function of organs such as the kidneys. Where we know the cancer drug is largely excreted through the kidneys. Clinical Outcome in this disease is still in a state of patients' usually continuing chemotherapy.

References

1. NCCN Clinical Practice Guidelines in Oncology. Bone Cancer. 2011 Version
2. Annmeik M van Maldegem1, Pancras CW Hogendoorn3 and Andrew B Hassan. The clinical use of biomarkers as prognostic factors in Ewing sarcoma. *Clinical Sarcoma Research* .2012, 2:7. http://www.clinicalsarcomaresearch.com/content/2/1/7.
3. Medicine, s cecil. Goldman (24th ed. ed.). Philadelphia: *Elsevier Saunders*. p. 1326. ISBN 978-1-4377-2788-3.
4. Iwamoto Y (February 2007). "Diagnosis and treatment of Ewing's sarcoma". Jpn*. J. Clin. Oncol*. 37 (2): 79–89. doi:10.1093/jjco/hyl142. PMID 17272319.
5. Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, Otter R, Licitra L, Mallone S, Tavilla A, et al: Rare cancers are not so rare: The rare cancer burden in Europe. *Eur J Cancer*.2011, 47:2493-2511.
6. Ghasemi A, Hiradfar AA, Pedram M. An Epidemiologic Study of Ewing Sarcoma Family at SHAFA Hospital in Khozestan Province-IRAN, a Referral Children Cancer Treatment Center. *Iranian Journal of Pediatric Hematology and Oncology* ,Vol1. No1.
7. Bernstein M, Kovar H, Paulussen M. Ewing sarcoma family of tumors: Current management . *The Oncologist* 2006,11(5):503-519.
8. Lanzkowsky P. Manul of pediatric hematology and oncology. 4th edition. California, USA, *Elsevier Inc*; 2005; pp:596-599.
9. Pizzo PA, Poplack DA. Principles and practice of pediatric oncology. 5th edition. UAS, Lippincott Williams & Wilkins; 2006; pp 1002-1009.
10. Worch J, Cyrus J, Goldsby R, Matthay KK, Neuhaus J, DuBois SG.
11. Parkin DM, Stiller CA, Draper GJ, et al. International incidence of childhood cancer, Vol. 2. Lyon: IARC (IARC Scientific Publications No 87); 1998.
12. Stiller CA, Bielack SS, Jundt G, et al. Bone tumours in European children and adolescents, 1978–1997. Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006; 42:2124–2135.
13. Little J. Epidemiology of Childhood Cancer. Lyon: IARC (IARC Scientific Publications No. 149); 1999.
14. Rachel Eyre, Richard G. Feltbower, Emmanuel Mubwandarikwa O.B. Eden, and Richard J.Q. McNally, Z. Review Epidemiology Of Bone Tumours In Children and Young Adults. Pediatr Blood Cancer. 2009;53:941–952.

15. Patel M, Simon JM, Iglesia MD, Wu SB, McFadden AW, Lieb JD, Davis IJ. Tumor-specific retargeting of an oncogenic transcription factor chimera results in dysregulation of chromatin and transcription. Genome Res. 2012 Feb;22(2):259-70. doi: 10.1101/gr.125666.111. *Epub* 2011 Nov 15.

16. Navarro D, Agra N, Pestaña A, Alonso J, González-Sancho JM. The EWS/FLI1 oncogenic protein inhibits expression of the Wnt inhibitor DICKKOPF-1 gene and antagonizes beta-catenin/TCF-mediated transcription. Carcinogenesis. 2010 Mar;31(3):394-401. doi: 10.1093/carcin/bgp317. *Epub* 2009 Dec 17.

17. López Guerra JL, Márquez-Vega C, Ramírez-Villar GL, Cabrera P, Ordóñez R, Praena-Fernández JM, Ortiz MJ. Prognostic factors for overall survival in paediatric patients with Ewing sarcoma of bone treated according to multidisciplinary protocol. *Clin Transl Oncol.* 2012 Apr;14(4):294-301. doi: 10.1007/s12094-012-0798-y.

18 Tural D, Molinas Mandel N, Dervisoglu S, Oner Dincbas F, Koca S, Colpan Oksuz D, Kantarci F, Turna H, Selcukbiricik F, Hiz M. Extraskeletal Ewing's sarcoma family of tumors in adults: prognostic factors and clinical outcome. *Jpn J Clin Oncol.* 2012 May;42(5):420-6. doi: 10.1093/jjco/hys027. Epub 2012 Mar 12.

19 Huang KL, Chen CF, Wu PK, Chen PC, Chen WM, Liu CL, Chen TH**.** Clinical outcomes and prognostic factors of Ewing sarcoma: a clinical analysis of 12 patients in Taiwan. *J Chin Med Assoc.* 2012 Jan;75(1):16-20. doi: 10.1016/j.jcma.2011.10.013. Epub 2011 Dec 1

20 Koohbanani B, Han G, Reed D, Zhao Q, Yi D, Henderson-Jackson E, Bui MM. Ethnicity and age disparities in Ewing sarcoma outcome. *Fetal Pediatr Pathol.* 2012 Oct 8.

21 Parida L, Fernandez-Pineda I, Uffman J, Navid F, Davidoff AM, Neel M, Krasin MJ, Rao BN. Clinical management of Ewing sarcoma of the bones of the hands and feet: a retrospective single-institution review. *J Pediatr Surg.* 2012 Oct;47(10):1806-10. doi: 10.1016/j.jpedsurg.2012.05.022.

22 Raciborska A, Bilska K, Rogowska E, Godziński J, Wożniak W. Surgical treatment of patients with disseminated Ewing sarcoma in our clinical experience. *Ortop Traumatol Rehabil.* 2011 May-Jun;13(3):271-7.

23 Mora J, de Torres C, Parareda A, Torner F, Galván P, Rodríguez E, Cardesa T, Salvador H, Suñol M, Huguet R, Cruz O. Treatment of Ewing sarcoma family of tumors with a modified P6 protocol in children and adolescents. *Pediatr Blood Cancer.* 2011 Jul 15;57(1):69-75. doi: 10.1002/pbc.22813. Epub 2011 Mar 7.

24 Olmos D, Postel-Vinay S, Molife LR, Okuno SH, Schuetze SM, Paccagnella ML, Batzel GN, Yin D, Pritchard-Jones K, Judson I, Worden FP, Gualberto A, Scurr M, de Bono JS, Haluska P. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. *Lancet Oncol.* 2010 Feb;11(2):129-35. doi: 10.1016/S1470-2045(09)70354-7. Epub 2009 Dec 23.

25 Gaetano Bacci, Stefano Ferrari, Franco Bertoni, Simonetta Rimondini, Alessandra Longhi, Patrizia Bacchini,Cristiana Forni, Marco Manfrini, Davide Donati, and Piero Picci. Prognostic Factors in Nonmetastatic Ewing's Sarcoma of Bone Treated With Adjuvant Chemotherapy: Analysis of 359 Patients at the Istituto Ortopedico Rizzoli. *JCO*, Vol 18, No 1 (January), 2000: pp 4-11

26 Letson, G. D.; Greenfield, G. B.; and Heinrich, S. D**.:** Evaluation of the child with a bone or soft-tissue neoplasm. *Orthop. Clin. North America,* 27: 431-451, 1996.

27 Simon, M. A., and Finn, H. A.: Diagnostic strategy for bone and soft-tissue tumors. *J. Bone and Joint Surg.,* 75-A: 622-631, April 1993.

28 Frassica, F. J.; Frassica, D. A.; Pritchard, D. J.; Schomberg, P. J.; Wold, L. E.; and Sim, F. H.: Ewing sarcoma of the pelvis. Clinicopathological features and treatment. *J. Bone and Joint Surg.,* 75-A: 1457-1465, Oct. 1993.

29 13. Vlasak, R., and Sim, F. H.: Ewing's sarcoma. *Orthop. Clin. North America,* 27: 591-603, 1996.

30 Björn Widhe, M.B. , And Torulf Widhe, M.D. Initial Symptoms and Clinical Features in Osteosarcoma and Ewing Sarcoma. *The Journal of Bone and Joint Surgery, Incorporated*. Vol. 82-A, No. 5, May 2000.

31 Buckley JD, Pendergrass TW, Buckley CM, Pritchard DJ, Nesbit ME, Provisor AJ and Robison LL. Epidemiology of osteosarcoma and Ewing's sarcoma in childhood: A study of 305 cases from the Children's Cancer Group. Cancer. Cancer 1998;83:1440-8.

32 Gurney JG, Severson RK, Davis S, and Robison LL. Incidence of cancer in children in the United States. Cancer 1995;75:2186-2195.

33 Polednak AP. Primary bone cancer incidence in black and white residents of New York state. Cancer 1985;55:2883-2888.

34 Mashhadi MA, Kaykhaei MA, Sanadgol H. Low prevalence of high-dose methotrexate nephropathy in patients with malignancy. Iran J Kidney Dis. 2012 Mar;6(2):105-9.

35 NCCN Clinical Practice Guidelines in Oncology. Cancer and Chemotherapy Induced Anemia. 2010 Version 2.

36 Bucholtz J. Comforting children during radiotherapy.*Oncology Nursing Forum* 1994,21(6): 987-993.

37 Hartsock, J. Ewing's sarcoma: The Uncommon Bone Cancer. Perspectives Recovery Strategies from the OR to Home, Vol. 2 No.4.

38 National Spinal Cord Injury Association Resource Center Fact Sheet #2

39 Kai-Ling Huang , Cheng-Fong Chen , Po-Kuei Wu*, et.all*. Clinical outcomes and prognostic factors of Ewing sarcoma: A clinical analysis of 12 patients in Taiwan. Journal of the Chinese Medical Association 75 (2012).

40 Rosen G, Caparros B, Huvos AG, Cynthia Kosloff MS, Anita Nirenberg RN, Adrienne Cacavio RN, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy.Cancer 1982;49:1221e3.

AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.