# OSTEOSARCOMA: PROGNOSIS AFTER STANDARD MANAGEMENT AND FACTOR RELATED TO GOOD PROGNOSIS

**Abdul Qadir Khan, Mubashar Ahmed Bajwa, Muhammad Jameel, Hafiz Muhammad Yaqoob, Naveed Ullah Khan, Syed Asim Sherazi**

Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

## ABSTRACT

***Objective:*** To study the prognosis of osteosarcoma and factor related to good prognosis among patients managed at a tertiary care Military Hospital.

***Study Design:*** Retrospective case series.

***Place and Duration of Study:*** Department of Orthopedics and Pathology, CMH Hospital Rawalpindi, fro, 2010 to 2016.

***Methodology:*** A total of 42 patients with histological diagnosis of osteosarcoma were picked up from the registers of Armed forces institute of pathology who were managed (neo-adjuvant chemotherapy, surgery and post-operative chemotherapy) at orthopedics and oncology department of Combined military hospital RWP. Patients were called on the telephone numbers mentioned in the register and two year status of disease along with socio-demographic data was recorded.

***Results:*** Out of 42 patients with osteosarcoma included in the study, 24 (57.1%) had good prognosis while 18 (42.9%) had either died or were living with the disease. Low grade on Huvos grading and size of tumor <8cm had a statistically significant relationship with presence of good prognosis in the study population.

***Conclusion:*** This study showed that after the standard management of osteosarcoma with neoadjuvant chemo-therapy, surgery and post-surgical chemotherapy the prognosis remains variable after two years. Tumors with smaller size and low grade at the time of diagnosis may have a good two ear prognosis.

**Keywords:** Osteosarcoma, Prognosis, Factors.



## INTRODUCTION

Epidemiology of cancers has been changing all around the world in past few years due to modern techniques to diagnose this lethal illness[1]. Almost all he cancers of the body have shown rise in their incidence in last decade in all parts of the world[1]. Bone tumors have been no exception to this rule. Both benign and malignant tumors have been diagnosed frequently all around the globe in last few years. Osteosarcoma is one of the commonest primary bone tumors which involve multidisciplinary approach for diagnosis and management[2].

As diagnostic modalities have modernized and both radiology and laboratory techniques have created a revolution in diagnostic aspects of oncology, management guidelines have also been in evolving phase in current era. Researchers and clinicians have been trying to find out new and more efficacious ways to combat the lethality of cancer[3]. Osteosarcoma has been also managed by various members of medical tam in number of ways. Chemotherapy (before and after the surgery) and surgery being the main stay of management and may offer the patient good number of disease free years in a lot of cases[4].

Despite the evolving nature of therapeutic modalities for osteosarcoma, still the prognosis is variable among the sufferers and depends upon number of factors[5]. Zhang *et al* published a review in 2018 that summarized the current studies surrounding progress in the chemotherapeutic treatment of osteosarcoma and discussed the advantages and potential feasibility of Docetaxel+ gemcitabine in the treatment of this malignant condition[6]. Back in 2000 Bacci *et al* published a paper with an objective to look for

**Correspondence: Dr Abdul Qadir Khan,** House No. 903, Street No 105, G-9/4 Islamabad, Pakistan *(Email: qadirafridi85@gmail.com)*
*Received: 10 Apr 2018; revised received: 10 Aug 2018; accepted: 15 Aug 2018*

the outcome or prognosis of patients suffering from osteosarcoma with an experience of 10 years with the patients. They concluded that chemotherapy especially aggressive approach with that may reduce amputations and may even cure the disease in majority of patients. Side effects of chemotherapies, secondary tumors or recurrences may occur in long run therefore more studies with long follow up period may show better results[7]. Ali *et al* in 2019 studied similar aspect of this malignant condition in the pediatric population and revealed that prognosis does not differ in the developed and the developing countries if multidisciplinary approach is followed and local control of disease and degree of necrosis at time of presentation may predict the treatment response and affect the long term prognosis in this condition[8]. An Irish study comprising of experience of 26 years of a center concluded that patients with osteosarcoma have similar long term outcome and prognosis as that of patients in other parts of the world. Age of the patient and stage of the illness at time of diagnosis ma have a significant impact on the prognosis of these patients[9].

Multidisciplinary efforts for management of various malignancies is at toddler stage in our part of the world. We use most of the guidelines based upon the experience of western populations. A local study has been done in order to find the epidemiological parameters of osteosarcoma ant it revealed that Karachi, a big city of Pakistan has been a region with high prevalence of patients suffering from bone sarcomas. They stated that these tumors have been more common in young age group and among the males[10]. Therefore it is high time to look into our practises regarding the management of osteosarcoma and its effect on long term outcome and prognosis of the patients suffering from this condition.

## METHODOLOGY

This case series was conducted at CMH and AFIP Rawalpindi from 2010 to 2016. Nonprobability Consecutive sampling technique was applied to enroll the sample population for this case series which was retrospective regarding the recruitment of patients from the registers. Patients of both genders with osteosarcoma diagnosed by consultant histopathologist as per set criteria[11] between the age of 18 and 60 were enrolled for this case series. Patients with secondary bone malignancies or other medical illnesses with lethal potential or those who could not complete the standard management (neoadjuvant chemotherapy, surgery and post-surgical chemotherapy) were part of the exclusion criteria. Those whose clear follow up or health status two years after the management was not possible were also not included in our study.

Ethical review board committee of the hospital was approached to get the ethical approval for this study. Patients were followed up from the register who were diagnosed as osteosarcoma based on the histopathology findings and then under went three cycles of neo adjuvant chemotherapy with high doses of methotrexate, Adriamycin, ifosfamide and cisplatin. After definitive surgery six more cycles of chemotherapy were administered to the patients. Two year after this management plan their status was recorded and taken as the prognosis[12]. Good prognosis was considered if they were having a disease-free life. Bad prognosis was considered if they had died or were still living with the disease. The prognosis status was established after detailed history from the patient and reviewing the latest investigations. News of death from the first degree relative or viewing of death certificate was considered suffice to establish the death of the patient. A proforma was designed to incorporate all the relevant socio-demographic and illness related factors including the age, gender, size of tumor and Huvos grade[13] of the tumor at the time of diagnosis.

Characteristics of participants and the distribution of the patients with prognosis after the standard management were described by using the descriptive statistics. Chi-square was applied to look for the correlation of age, gender, size of tumor and Huvos grade with the presence of good prognosis. Once correlation was established then extent of correlation was determined by

the binary logistic regression analysis. All statistical analysis was performed using Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Differences between groups were considered significant if *p*-values ≤0.05.

## RESULTS

Target population was all the osteosarcoma patients found in the register of AFIP. Follow up protocol and application of exclusion and inclusion criteria made the sampling frame small and only 42 patients could be recruited for the study in the given time period. Out of these 42, 31 (73.8%) were male while 11 (26.2%) patients were male. Table-I shows that out of 42 patients of osteosarcoma followed up, 24 (57.1%) had good prognosis after the standard management while 18 (42.9%) had poor prognosis despite the neo-adjuvant chemotherapy. Table-II shows that Low grade on Huvos grading and size of tumor <8cm had a statistically significant relationship (*p*-value <0.05) with presence of good prognosis in the study population upon application of binary logistic regression analysis.

**Table-I: Outcome of various variables studied in the analysis: Chi-square test.**

| Factors studied | Good prognosis | Poor prognosis | *p*-value |
|---|---|---|---|
| **Age** | | | |
| <30 years | 14 (88.9%) | 16 (21.4%) | 0.024 |
| >30 years | 10 (11.1%) | 02 (78.6%) | |
| **Gender** | | | |
| Male | 19 (41.7%) | 12 (28.6%) | 0.364 |
| Female | 05 (58.3%) | 06 (71.4%) | |
| **Size of Tumor** | | | |
| <8 cm | 16 (52.7%) | 02 (71.4%) | <0.001 |
| >8 cm | 08 (47.3%) | 16 (28.6%) | |
| **Huvos Grading** | | | |
| I & II | 21 (91.7%) | 04 (50%) | <0.001 |
| III & IV | 03 (8.3%) | 14 (50%) | |

**Table-II: The correlated factors relating to presence of good prognosis in patients of osteosarcoma after standard management: the binary logistic regression analysis.**

| | *p*-value | Odds Ratio | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age (ref. is <30 years) | 0.118 | 0.118 | 0.008 | 1.712 |
| Gender (reference is male) | 0.509 | 0.461 | 0.046 | 4.586 |
| Huvos grading (ref. is grade I & II) | 0.006 | 15.721 | 2.243 | 110.209 |
| Size of tumor (ref. is <8 cm) | 0.013 | 18.997 | 1.878 | 192.192 |

## DISCUSSION

Management of cancer has been a challenge for clinicians of various medical specialties. Though oncology is an evolving field and involves the radiation and medical treatment of this devastating illness but still all other specialties are also directly or indirectly linked with adequate management. Despite a lot of efforts many of the malignant conditions still have poor prognosis and length and quality of life really become affected after the diagnosis even with the treatment. Patients with osteosarcoma have been looked upon with this perspective in some studies. A study conducted in our art of the world reflecting the experience of the team from a tertiary care oncology set up of Pakistan concluded that cisplatin/doxorubicin combination when combined with surgery proved to be a better option for adult patients suffering from osteosarcoma. Authors remained uncertain regarding the role of methotrexate in this regard[14]. This study was published in 2014 after which a lot of other studies have also been published revolving around various chemotherapeutic agents including neo-adjuvant chemotherapy as well in order to find the best combination. We planned this study with the objective to study the prognosis of osteosarcoma and factor related to good prognosis among patients managed at a tertiary care military hospital.

Tsuda *et al* published a retrospective analysis in 2018 with objective to study the whole clinical spectrum with which patients with osteosarcoma pass through and to see the long-term prognosis with respet to age of the patient. They came up

with interesting findings that neoadjuvant chemotherapy had age related effect on the outcome of patients with osteosarcoma and patients with age more than 41 years may not get benefit from this option[15]. Our study also revealed that age has no statistically significant relationship with the treatment response or prognosis among the patients suffering from osteosarcoma.

The European and American Osteosarcoma Study (EURAMOS)-1 is a good effort with egard to analyze the long term prognosis of patients suffering from osteosarcoma. They concluded that tumor site has no role in determining the prognosis of the patients and 3 and 5 year survival rate with neoadjuvant chemotherapy an surgery has been good and depends upon the histological response of the tumor[16]. Our study generated similar findings as small tumor size and low grade on Huvos classification had a significant relationship with good prognosis but our study had no long term follow up which could pick up the recurrence or other complications which might have occurred after the two years.

Gender was not statistical significantly related to the treatment response in our study (*p*-value >0.05). Fukushima *et al* published a study on similar topic in 2018 with the objective to determine survival rates of bone sarcoma among young population in Japan[17]. Gender in that study had no statistical relationship with god prognosis but size of tumor had with *p*-value 0.05. Therefore, results from their study as well as our study highlight the fact that gender has no established role so far in predicting the prognosis of osteosarcoma but size of the tumor at time of diagnosis may be used as predictor of prognosis.

Wheelan *et al* published a study in 2012 to determine the optimum regimens for survival, toxicity and prognostic factors for patients suffering from osteosarcoma[18]. Comparison was made between doxorubicin 75 mg/m$^2$ and cisplatin 100 mg/m$^2$ vs methotrexate (BO02/ 80831), a multidrug regimen (BO03 / 80861) and a dose-intense schedule (BO06 / 80931). Both showed significant improvement and there was no statistically significant difference in response to both the regimens therefore authors could not recommend which one is better in this regard. Good histological response to preoperative chemotherapy, distal tumor location (all sites other than proximal humerus / femur) and female gender were the factors which came to be statistically significantly related to better long term outcome in their study[18]. Though their study was much larger in scope and sophisticated in methodology as compared to ours but still finings have been comparable.

This study has few limitations as well. Retrospective study design raises a lot of methodological issues. Patients who were lost to follow up may change the results altogether. Exact cause of death among the deceased was also not ascertained. More studies with better methodology and prospective study design with long follow up may yield better results which could help clinicians to ascertain the prognosis and factors affecting prognosis of this rare malignancy.

## CONCLUSION

This study showed that after the standard management of osteosarcoma with neoadjuvant chemotherapy, surgery and post-surgical chemotherapy the prognosis remains variable after two years. Tumors with smaller size and low grade at the time of diagnosis may have a good two ear prognosis.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69(1): 7-34.
2. Franchi A. Epidemiology and classification of bone tumors. Clin Cases Miner Bone Metab 2012; 9(2): 92-95.
3. Durfee RA, Mohammed M, Luu HH. Review of osteosarcoma and current management. Rheumatol Ther 2016; 3(2): 221-43.
4. Bielack SS, Hecker-Nolting S, Blattmann C, Kager L. Advances in the management of osteosarcoma. F1000 Res 2016; 5(1): 2767.
5. Misaghi A, Goldin A, Awad M, Kulidjian AA. Osteosarcoma: A comprehensive review. SICOT J 2018; 4(1): 12-9.
6. Zhang Y, Yang J, Zhao N, Wang C, Kamar S, Zhou Y, et al. Progress in the chemotherapeutic treatment of osteosarcoma. Oncol Lett 2018; 16(5): 6228-37.

7. Bacci G, Ferrari S, Bertoni F, Ruggieri P, Picci P, Longhi A, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. J Clin Oncol 2000; 18(24): 4016-27.
8. Abou-Ali B, Salman M, Ghanem KM, Boulos F, Haidar R, Saghieh S, et al. Clinical prognostic factors and outcome in pediatric osteosarcoma: Effect of delay in local control and degree of necrosis in a multidisciplinary setting in lebanon. J Glob Oncol 2019; 5(1): 1-8.
9. O'Kane GM, Cadoo KA, Walsh EM. Perioperative chemotherapy in the treatment of osteosarcoma: a 26-year single institution review. Clin Sarcoma Res 2015; 5(1): 17-9.
10. Bhurgri Y, Usman A, Bhurgri H, Faridi N, Bashir I, Bhurgri A, et al. Primary malignancies of bone and cartilage in Karachi. Asian Pac J Cancer Prev 2009; 10(5): 891-94.
11. Chui MH, Kandel RA, Wong M, Griffin MA, Bell RS, Blackstein ME, et al. Histopathologic features of prognostic significance in high-grade osteosarcoma. Arch Pathol Lab Med 2016; 140(11): 1231-42.
12. Wu C, Wang Q, Li Y. Prediction and evaluation of neoadjuvant chemotherapy using the dual mechanisms of 99mTc-MIBI scintigraphy in patients with osteosarcoma. J Bone Oncol 2019; 17(1): 100250.
13. Berhe S, Danzer E, Meyers P, Behr G, La-Quaglia MP, Price AP. Unusual abdominal metastases in osteosarcoma. J Pediatr Surg Case Rep 2018; 28(1): 13-6.
14. Imtiaz S, Kazmi A. Patterns of care and outcomes of adult osteosarcoma in a tertiary care cancer centre in Pakistan. J Pak Med Assoc 2014; 64(10): 1166-70.
15. Tsuda Y, Ogura K, Shinoda Y, Kobayashi H, Tanaka S, Kawai A. The outcomes and prognostic factors in patients with osteosarcoma according to age: a Japanese nationwide study with focusing on the age differences. BMC Cancer 2018; 18(1): 614-19.
16. Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn P, Krailo MD, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. Eur J Cancer 2019; 109(1): 36-50.
17. Fukushima T, Ogura K, Akiyama T, Takeshita K, Kawai A. Descriptive epidemiology and outcomes of bone sarcomas in adolescent and young adult patients in Japan. BMC Musculoskelet Disord 2018; 19(1): 297-99.
18. Whelan JS, Jinks RC, McTiernan A, Sydes MR , Hook JM , Trani L, et al. Survival from high-grade localised extremity osteosarcoma: combined results and prognostic factors from three European Osteosarcoma Intergroup randomised controlled trials. Ann Oncol 2012; 23(6): 1607-16.