

Research Article

Experience from Cancer Registry of a Developing Country Regarding Quality of Care and Non-Compliance among Osteosarcoma Patients

Badaruddin Sahito¹, Sheikh Muhammad Ebad Ali^{*1}, Mustafa Saleem², Noor Muhammad Soomro³, Muhammad Soughat Katto⁴, Asif Jatoi⁴

¹Department of Orthopedic and Surgery, Dow University of Health Sciences, Karachi, Pakistan.

²Department of UGME, Dow University of Health Sciences, Karachi, Pakistan.

³Department of Oncology, Dr. Ruth KM Pfau Civil Hospital Karachi, Pakistan.

⁴Department of Orthopedic and Surgery, Dr. Ruth KM Pfau Civil Hospital Karachi, Pakistan.

Abstract: In this study, we evaluated the level of care given by our institution and to assess the non-compliance along with predictor for non-compliance among osteosarcoma patients.

Materials and Methods: The included participants were proven for osteosarcoma after biopsy between January 2014 to December 2020. Records were searched from Departmental Cancer Registry for details regarding treatment plans and follow-ups. The data of outcomes were compared with the standard guidelines. Patients who did not attend follow-ups, surgery or chemotherapy were termed as non-compliant. The patients or their next of kins were inquired about the factors behind non-compliance.

Results: 46 participants with 34 (74.9%) males and 12 (26.1%) females and a mean age of 19.7 ± 9.7 years were included. The prescribed treatment plan was followed by 11 (23.91%) patients. Neoadjuvant and adjuvant chemotherapy were taken by 18 (39.13%) and 10 (21.74%) candidates, respectively. Surgery was performed in 22 (44.9%). The patients who did not received chemotherapy was attributed to affordability ($P=0.008$) and patients' or next to kins' choices ($P=0.02$) while age ($P=0.039$), patients' consent not given (78.3%; $P=0.05$), and stage II (52.2%; $P=0.048$) were predictors of surgical non-compliance.

Conclusion: We conclude that the care deferred significantly from the guidelines regarding surgery and chemotherapy. Age, affordability, late stage, and personal choices are the significant predictors for non-compliance for chemotherapy and surgery.

Keywords: Osteosarcoma, Bone tumors, Appraisal, Cancers, Chemotherapy, Surgery.

INTRODUCTION

Osteosarcoma has been the most common malignant tumor involving long bones mostly [1]. The disease involves a bimodal age distribution with a higher incidence in pediatric and adolescent group [1]. From a worldwide epidemiological study conducted in 2009, an incidence of 4-9 million cases of osteosarcoma was found with higher incidence in males [2]. The burden of disease has been dramatically higher in certain countries making a possible genetic linkage [1]. Histologically, tumor is based on overgrowth of epithelioid, plasmacytoid, spindled, small round cells, clear cells, giant tumor cells with lace-like disorganized woven bone [3]. Osteosarcoma has been treated successfully with a multidisciplinary approach involving surgery, chemotherapy, and occasionally radiotherapy [4, 5]. The approach has led to success in terms of limb salvage surgery becoming a possibility while has also increased the life expectancy of osteosarcoma survivors.

Guidelines focusing on management of osteosarcoma has been proposed which include guidelines by National Compre-

hensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), European Reference Network for Paediatric Cancers (PaedCan), and European Network for Rare Adult Solid Cancer (EURACAN) [6]. Similarly, multiple chemotherapeutic regimens have been proposed to regress the tumor which includes Cisplatin + Doxorubicin regimen, MAP regimen, MAPIE, and MAP-I regimen [7, 8]. A study from developed country showed that mortality rate dropped significantly in last 10 years as they abided strictly by these guidelines [9]. But studies from developing nations potentially attributed non-compliance for decreased five-year survival and increased mortality, incidence of metastasis, and amputations/disarticulations.

We found one study by Bajpai *et al.* focusing upon the assessment of factors related with non-compliance among osteosarcoma patients and audit of quality of institutional osteosarcoma-related care [10]. Hence, the aim of this study is to compare the standard of care provided by the institution with the NCCN and MAP guidelines and factors contributing to non-compliance with the treatment plans among patients with osteosarcoma. We further aim to appraise the standard of care given to the patients by implementing measures to avoid

*Address correspondence to this author at the Department of Orthopedic and Surgery, Dow University of Health Sciences, Karachi, Pakistan.
Email: sheikh.muhammadebadali14@dmc.duhs.edu.pk

future lost to follow-up and non-compliance.

MATERIALS AND METHODS

After obtaining departmental permission, we contacted the patients from registry to get consent for enrolment in the study. Records obtained were regarding the age, gender, grade of tumor, duration of follow-up, chemotherapy cycles, surgical procedures, and duration of death after diagnosis. We ensured to maintain the anonymity of each patient.

The included participants were proven for osteosarcoma after biopsy between January 2014 to December 2020. Records were searched from Departmental Cancer Registry for details regarding treatment plans and follow-ups. Those patients or next to kins were communicated by data collectors for inquiry about general well-being status, compliance with the current treatment, and reasons for lost to follow-up or non-compliance with the prescribed treatment plan. Lack of follow-up, lack of adherence to drug regimen, or avoidance of surgery were termed as poor compliance. The responses were documented on a newly introduced proforma in patient files to evaluate the standard of care being provided.

Patients who had clinical or radiological evidence without biopsy were excluded from the study. Missing records, unresponsiveness, undocumented or unclear treatment planned patients, and those who did not give consent did not qualify for inclusion.

National Comprehensive Cancer Network (NCCN) guideline was used as standard with which our compliance was compared. Factors were evaluated for non-compliance with the proposed treatment plan including chemotherapy and surgery as quoted by patients or their next to kins. Factors including age, gender, patients' choice, affordability, pain/swelling/fracture at presentation, staging of osteosarcoma by Enneking staging system and treatment pursued elsewhere were assessed by statistical analysis to predict the non-compliance.

STATISTICAL ANALYSIS

IBM SPSS version 22.0 was utilized for statistical analysis. Mean (standard deviation) and frequencies (percentage) of patient's data were used for continuous and categorical data, respectively. An ordinal regression analysis was performed to predict the relation between categorical non-compliance data with each baseline characteristic and further using goodness-of-fit to find the statistical significance of the model. Multiple regression was performed for relation between continuous non-compliance data using ANOVA for statistical significance of the model. The confidence interval remained 95% and significance remained two-tailed for all tests.

RESULTS

We found 48 participants who were treated for osteosarcoma in our institution. Out of these 48, 46 (95.83%) fulfilled the inclusion and exclusion criteria. The study population included 34 (73.9%) males and 12 (26.1%) females with mean age 19.7 ± 9.7 years. Out of these candidates, 10 (21.74%) patients were alive while other 30 (65.23%) patients died within 3 years after the diagnosis. After analysis, only 11 (23.91%) participants received treatment according to NCCN guidelines where chemotherapy and surgery were completed with regular follow-ups while rest of the patients did not receive either surgery or chemotherapy or both after the diagnosis. These characteristics are shown in Table 1.

Table 1. Baseline Characteristics of Each Patient.

Characteristic	
Age in years	19.69 (9.7)
Gender	
Male	34 (73.9%)
Female	12 (26.1%)
Stage	
Stage I	10 (21.7%)
Stage II	24 (52.2%)
Stage III	12 (26.1%)
Consent/Patient choice	
Yes	10 (21.7%)
No	36 (78.3%)
Presentation	
Pain	11 (23.9%)
Swelling	11 (23.9%)
Fracture	24 (52.2%)
Treated elsewhere	
Yes	5 (10.9%)
No	41 (89.1%)
Affordability issues	
Yes	15 (32.6%)
No	31 (67.4%)
End stage illness	
Yes	14 (30.4%)
No	32 (69.6%)

Non-compliance with Chemotherapy

The results have shown that the mean cycles of neoadjuvant chemotherapy administered were 1.41 (1.2) cycles. A total of 18 (39.13%) candidates received neoadjuvant chemotherapy where 5 (10.9%) candidates got three-cycles, 8 (17.4%) received four-cycles, and 3 (6.5%) received six-cycles as summarized in Fig. (1). We assessed the independent variables by multiple linear regression analysis to predict the cause of poor compliance rates among our patients where statistically significant predictors were unaffordability of drugs ($\beta=-0.25$, $P=0.008$) and patients' or next to kins' choices ($\beta=0.48$, $P=0.02$) which were the strongest predictor while presentation ($\beta=0.25$, $P=0.089$) remained a strong but nonsignificant factor.

The mean cycles of adjuvant chemotherapy administered were 0.85 (0.12) cycles. A total of 10 (22.73%) candidates received adjuvant chemotherapy where 6 (13.0%) received four-cycles while 1 (2.2%) candidate received one-cycle,

three-cycles, five-cycles, and six-cycles each as summarized in Fig. (2). We performed multiple linear regression but none of the factors were found significant.

Non-compliance with Surgery

22 (44.9%) candidates received surgery for osteosarcoma. 12 (26.1%) patients underwent limb salvage surgery while 10 (21.7%) patients received amputation or disarticulation. Among three candidates who are included in amputation or disarticulation subgroup, limb salvage surgery was initially attempted but amputation was later performed due to recurrence of tumor. The statistically significant factors affecting non-compliance with surgery were age ($OR=0.07$; 95% $CI=0.003-0.15$; $P=0.039$), patients' consent not given ($OR=-1.78$; 95% $CI=1.12-2.76$; $P=0.05$), and stage II ($OR=3.31$; 95% $CI=0.45-6.18$; $P=0.024$). Other predictors that were not statistically significant are swelling ($OR=1.45$; 95% $CI=-0.4-3.3$; $P=0.06$) on presentation and end stage illness ($OR=-2.04$; 95% $CI=-4.11-0.04$; $P=0.08$).

Neoadjuvant Chemotherapy cycles

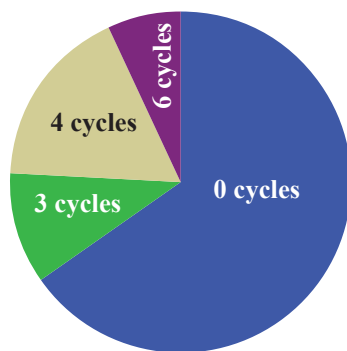


Fig. (1). Neoadjuvant Chemotherapy Cycles in Pie-chart.

Adjuvant Chemotherapy cycles

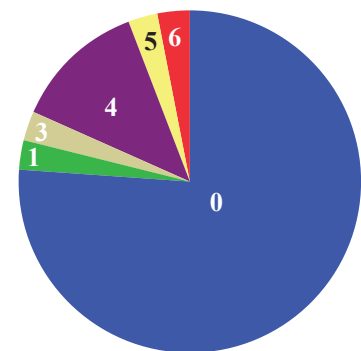


Fig. (2). Adjuvant Chemotherapy Cycles in Pie-chart.

Table 2. Summary of Management Plan from NCCN and MAP regimen [7,8].

Stage	Management	MAP Regimen
Stage 1a	Limb salvage surgery	On week 1, 4, 5, 9, and 10 (Neoadjuvant). On week 15, 16, 20, 21, 24, 25, and 29 (Adjuvant).
Stage 1b	Limb salvage surgery	
Stage 2a	Limb salvage surgery	
Stage 2b	Limb salvage surgery (Responsive to chemotherapy + good functions)	
	Amputation surgery (unresponsive to chemotherapy or bad functions)	
Stage 3 (Metastatic)	Limb salvage surgery (responsive to chemotherapy + metastasis controllable + good function)	On week 4, 5, 9, 10, 15, 16, 20, 21, 24, 25, 28 and 29
	Amputation surgery (unresponsive to chemotherapy or metastasis uncontrollable or bad function)	
Recurrent	Amputation surgery	

DISCUSSION

Osteosarcoma management has changed drastically in the past two decades adjoining multidisciplinary approach for cancer-care. The primary objective of this study was to assess the factors contributing to poor compliance and the quality of care offered in our institute. We have divided the compliance into two portions based on chemotherapy and surgery because of the referral system that involves referring the patient to specialized chemotherapy centers before and after surgery. This system has been implemented due to the lack of oncological tumor surgery centers. The treatment recommended under NCCN guidelines and MAP regimen are summarized in Table 2 as they were used as standard guidelines for treatment.

The results may show the most worrisome aspect where it showed significantly raised mortality compared to the studies from developed nations where osteosarcoma related 5-years survival has risen to 80% from 55% within two decades [11, 12]. We reported 65.23% three-years mortality in our study while the acceptable mortality rates in three-years across the world is below 25%. After analysis, we inferred that 76.09% of the participants were also non-compliant either with chemotherapy or surgery or both. This correlation became the key concept for further analysis for reasons behind this high non-compliance [13]. Another drawback seen from our data is the presentation of patients at late stages. Few participants presented at stage 1 while mostly presented with stage 2 and 3. 16% candidates already had metastasis to brain and lungs chiefly while 10% were suffering from end stage disease where surgery was not possible. A considerable number of patients reported for surgery had increase in swelling whereas they were alleviating the pain with OTC drugs and opioids. This explains the presentation on late stages as previous studies have proven swelling as a predictor of late stage [14].

From our results, the standard of care currently being offered to osteosarcoma patients are not comparable to the international standards as a significant population did not get the treatment as per the set measures. Moreover, a significant disruption is seen in chemotherapy cycles as majority of the patients did not receive any chemotherapy. However, a trend of higher neoadjuvant chemotherapy is observed compared to the adjuvant chemotherapy cycles. Similar trends were seen in previous studies regarding rectal cancers where more participants were compliant to neoadjuvant chemotherapy compared to adjuvant chemotherapy [15, 16]. The predictors that are contributing to this non-compliance in our case were either unaffordability or patients' choice. Newer chemotherapy regimens are the more cost effective yet these regimens are still costly for the developing countries [17]. This might be the possibility as most people are willing to take chemotherapy but could not afford it due to unavailability of resources as explained by few studies previously [18, 19]. A higher

number of adult patients who were above 60-years refused chemotherapy making patients' choice as another predictor. Furthermore, these patients were more likely to accept non-limb salvage surgery than limb salvage surgery due to sedentary lifestyles and less life expectancy. Similar results were discovered by Evans *et al.* and Longhi *et al.* in their study [20, 21].

Surgery has been adopted by more patients recently and slightly higher patients received limb salvage surgery than amputation/disarticulation. However, the standard compared to the previous epidemiological studies regarding surgical oncology of bones have shown a significant divergence as only less than 50% of the included participants received surgery. Due to the poor compliance with chemotherapy, a higher percentage of patients received non-limb salvage surgeries from our data than other studies. During analysis, we found several factors that were affecting the poor compliance with surgery among osteosarcoma patients. These included age, stage II, and patients' choice as significant variables directly associated with surgical compliance. The results signify that the patients who are adults and can make their own decisions are more likely to pursue with surgical treatment. Similar results were presented by Falkenstein *et al.* during analysis of compliance post liver transplant where younger participants were less compliant than older participants [22]. Moreover, we also found some variables which are strongly linked with surgical compliance but were not statistically significant. These included presentation with pain, swelling, and end stage illness preoperatively.

We conclude that the care deferred significantly from the guidelines regarding surgery and chemotherapy. Age, affordability, late stage, and personal choices are the significant predictors for non-compliance for chemotherapy and surgery. The factors affecting the non-compliance needs to be addressed.

Drastic measures need to be taken for further improving the quality of care offered to osteosarcoma patients. Health plans regarding better availability of drugs and counselling sessions for gaining patient consent are important measures. We also need to evaluate cost-effectiveness of chemotherapeutic regimens where more patients might be able to afford the drugs. Sessions with occupational and physical rehabilitation professionals are also necessary to further counsel the patients for postoperative management if needed.

AUTHORS' CONTRIBUTION

All authors' have contributed equally.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Sadykova LR, Ntekim AI, Muyangwa-Semenova M, *et al.* Epidemiology and risk factors of osteosarcoma. *Cancer Invest* 2020; 38(5): 259-69.
- [2] Mirabello L, Troisi RJ, Savage SA. International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. *Int J Cancer* 2009; 125(1): 229-34.
- [3] Yang C, Tian Y, Zhao F, *et al.* Bone Microenvironment and osteosarcoma metastasis. *Int J Mol Sci* 2020; 21(19): 6985.
- [4] Biazzo A, De Paolis M. Multidisciplinary approach to osteosarcoma. *Acta Orthop Belg* 2016; 82(4): 690-8.
- [5] Abbasi AN. Establishment and maintenance of quality of site-specific multidisciplinary tumor boards in Pakistan. *J Coll Physicians Surg Pak* 2016; 26(10): 805-7.
- [6] Casali PG, Bielack S, Abecassis N, *et al.* Bone sarcomas: ESMO-PaedCan-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29(Suppl 4): iv79-iv95.
- [7] Marina NM, Smeland S, Bielack SS, *et al.* Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): An open-label, international, randomised controlled trial. *Lancet Oncol* 2016; 17(10): 1396-408.
- [8] Biermann JS, Chow W, Reed DR, *et al.* NCCN guidelines insights: bone cancer, version 2. *J Natl Compr Canc Netw* 2017; 15(2): 155-67.
- [9] Yasin NF, Abdul Rashid ML, Ajit Singh V. Survival analysis of osteosarcoma patients: A 15-year experience. *J Orthop Surg (Hong Kong)* 2020; 28(1): 2309499019896662.
- [10] Bajpai J, Puri A, Shah K, *et al.* Chemotherapy compliance in patients with osteosarcoma. *Pediatr Blood Cancer* 2013; 60(1): 41-4.
- [11] Smeland S, Müller C, Alvegard TA, *et al.* Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders. *Eur J Cancer* 2003; 39(4): 488-94.
- [12] Bielack SS, Kempf-Bielack B, Delling G, *et al.* Prognostic factors in high-grade osteosarcoma of the extremities or trunk: An analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol* 2002; 20(3): 776-90.
- [13] Restrepo DJ, Huayllani MT, Boczar D, *et al.* Which factors affect survival in patients with upper limb osteosarcoma? *Anticancer Res* 2019; 39(9): 5027-31.
- [14] Clark JC, Dass CR, Choong PF. A review of clinical and molecular prognostic factors in osteosarcoma. *J Cancer Res Clin Oncol* 2008; 134(3): 281-97.
- [15] Xu Z, Mohile SG, Tejani MA, *et al.* Poor compliance with adjuvant chemotherapy use associated with poorer survival in patients with rectal cancer: An NCDB analysis. *Cancer* 2017; 123(1): 52-61.
- [16] Kasi A, Abbasi S, Handa S, *et al.* Total neoadjuvant therapy vs standard therapy in locally advanced rectal cancer: A systematic review and meta-analysis. *JAMA Netw Open* 2020; 3(12): e2030097.
- [17] Verma P, Jain S, Kapoor G, Tripathi R, Sharma P, Doval DC. IAP chemotherapy regimen is a viable and cost-effective option in children and adolescents with osteosarcoma: A comparative analysis with map regimen on toxicity and survival. *J Pediatr Hematol Oncol* 2021; 43(4): e466-e71.
- [18] Lentz R, Benson AB, 3rd, Kircher S. Financial toxicity in cancer care: Prevalence, causes, consequences, and reduction strategies. *J Surg Oncol* 2019; 120(1): 85-92.
- [19] Rothenberg ML, McCarthy J, Holmes P. Price, cost, and value of cancer medicines: A pharmaceutical industry perspective. *Cancer J* 2020; 26(4): 281-6.
- [20] Evans DR, Lazarides AL, Visgauss JD, *et al.* Limb salvage versus amputation in patients with osteosarcoma of the extremities: An update in the modern era using the National Cancer Database. *BMC Cancer* 2020; 20(1): 995.
- [21] Longhi A, Errani C, Gonzales-Arabo D, Ferrari C, Mercuri M. Osteosarcoma in patients older than 65 years. *J Clin Oncol* 2008; 26(33): 5368-73.
- [22] Falkenstein K, Flynn L, Kirkpatrick B, Casa-Melley A, Dunn S. Non-compliance in children post-liver transplant. Who are the culprits? *Pediatr Transplant* 2004; 8(3): 233-