Prognostic Modeling for Bone Sarcomas based on a Large Prospective Cohort from a Tertiary Care Cancer Centre in India

Laboni Sarkar\textsuperscript{1}, Jyoti Bajpai\textsuperscript{1}, Sushmita Rath\textsuperscript{1}, Akash Pawar\textsuperscript{1}, Arun Chandrasekharan\textsuperscript{1}, Goutam Panda\textsuperscript{1}, Dharmal Jakar\textsuperscript{1}, Jaya Ghosh\textsuperscript{1}, Siddhartha Laskar\textsuperscript{2}, Bharat Rekhi\textsuperscript{1}, Nehal Khanna\textsuperscript{2}, Jifmi Manjali\textsuperscript{2}, Mukta Ramdawar\textsuperscript{1}, Nilendu Purandare\textsuperscript{1}, Prabhat Bhargava\textsuperscript{1}, Nivedita Chakraborty\textsuperscript{3}, Kunal Gala\textsuperscript{3}, Yogesh Kembhavi\textsuperscript{1}, Venkatesh Rangarajan\textsuperscript{1}, Sripad Banavali\textsuperscript{1}, and Sudeep Gupta\textsuperscript{1}

\textsuperscript{1}Homi Bhabha National Institute
\textsuperscript{2}Tata Memorial Centre Department of Radiation Oncology
\textsuperscript{3}Tata Memorial Centre Department of Radiodiagnosis

March 21, 2024

Abstract

Background: Outcomes of adolescents and young adults (AYA) with bone sarcomas inclusive of osteosarcoma (OGS) and Ewing’s sarcoma (ES) are impacted by various factors including inadvertent prior treatment and poor compliance. We aimed to identify prognostic factors and derive prognostic models for these patients. Methods: All AYA OGS and ES cases treated at our institute with the “OGS-12” and Ewing’s family of tumors-2001 (“EFT-2001”) protocols from 2011 to 2021, and 2013 to 2018 respectively, were prospectively analyzed. Results: Among 606/748 (81.0%) AYA with non-metastatic osteosarcoma, significant factors included in the prognostic model were failure to complete protocol (hazard ratio (HR) 2.65, 95% confidence interval (CI) 1.65-4.26), prior treatment (HR 2.93, CI 1.4-6.1), necrosis $<90\%$ (HR 1.63, CI 1.24-2.1), joint involvement (HR 2.0, CI 1.49-2.69) and SAP $>\text{median (204 U/l)}$ (HR 1.63, CI 1.24-2.14). Of 104/263 (39.5%) AYA ES, significant factors were failure to complete protocol (HR 2.84, CI 1.03-7.8), prior treatment (HR 6.37, CI 1.8-22.0), necrosis $<100\%$ (HR 8.73, CI 2.16-35.3), and tumor size $>8\text{cm}$ (HR 2.64, CI 1.04-6.7). For 142/366 (38.8%) AYA with metastatic OGS, significant factors were failure to complete protocol (HR 5.29), metastases not amenable to local treatment (HR 1.96), necrosis $<90\%$ (HR 1.96), and $>10$ metastases (HR 2.44). For 38/82 (43.6%) AYA with metastatic extremity ES, significant factors were failure to complete protocol (HR 3.88) and metastases not amenable to local treatment (HR 10.6). Conclusion: We developed simple, effective prognostic models for AYA with bone sarcomas with wide applicability in LMIC.

Introduction:

Bone sarcomas inclusive of osteosarcoma (OGS) and Ewing’s sarcoma (ES) are rare, aggressive yet chemosensitive tumors with variable survival rates in Low and Middle-Income Countries (LMIC). There are various factors including delayed presentation with advanced disease and higher rates of metastatic disease, inadvertent prior treatment by primary care physicians, high dropout rates and poor adherence due to socioeconomic constraints with resultant compromised outcomes. Non-High-Dose-Methotrexate (Non-HDMTX) based regimens for osteosarcoma have gained popularity in these regions due to ease of administration on daycare basis, low cost and convenience. Therefore, finding valuable prognostic factors specifically targeting LMIC is crucial for predicting high-risk patients and early intervention to improve survival rates.

Among patients with osteosarcoma, possible prognostic factors, tumor size, metastatic disease at the time of diagnosis, histological grade, histologic response to neoadjuvant chemotherapy (NACT), and adequate surgical margins have consistently shown a strong correlation with survival. [1-2] Non-uniformity of chemotherapy
protocols for osteosarcoma preclude generalisability of results. We have previously published our experience with our institutional standard low cost, non-HDMTX based “OGS-12” protocol where serum alkaline phosphatase level for EFS and performance status for OS were found to be independent prognosticators, concordant with other reports, including those from India [3-6]. Histological response to NACT was an independent predictor of both EFS and OS which is also well-established.

For Ewing’s sarcoma, multiple prognostic factors have been reported, such as age, gender, localization, volume and size of the primary tumor, presence of metastasis, treatment regimens, a baseline level of hemoglobin or lactate dehydrogenase, and pathologic response to neoadjuvant chemotherapy [7-9]. In our published data on patients with Ewing’s sarcoma at our institute treated with the “EFT-2001” protocol, statistically significant prognostic factors included longer symptom duration, >= 99% necrosis, and protocol completion. [10]

There are unique challenges with rare cancers like bone sarcomas globally and a prognostic model with wide applicability including for the patients in LMIC wherein including social challenges also play a role is an unmet need. Special challenges in LMIC include lack of awareness among patients and primary health care providers with resultant delayed presentation, upstaging and high tumor burden.

We have aimed to identify prognostic factors including those specific to LMIC. Additionally, we have derived and validated a prognostic score for osteosarcoma that integrates biologic and social factors and is tailored for patients from an LMIC setting using a non-HDMTX-based protocol.

Methods:

All adolescent and adult OGS and ES cases treated at Tata Memorial Centre, Mumbai, with the “OGS-12” and Ewing’s family of tumors-2001 (“EFT-2001”) protocol from November 2011 to January 2021, and January 2013 to November 2018 respectively were prospectively analyzed separately. The “OGS-12” protocol consists of doublets of doxorubicin, ifosfamide and cisplatin given sequentially for eight cycles in both neoadjuvant (NACT) and adjuvant (ACT) settings. The “EFT-2001” protocol consists of a 12-month course of ifosfamide plus etoposide and vincristine, doxorubicin plus cyclophosphamide. Demographic factors recorded were age, gender and nutritional parameters. Disease factors were symptom duration, lactate dehydrogenase (LDH), serum alkaline phosphatase (SAP), tumor size, presence and sites of metastases, pathological fracture and neurovascular bundle involvement. Patients were stratified based on age into the following categories: 15-25 and >25-39 to evaluate prognostic significance of age. Patients with metastatic disease were stratified into categories based on number (<10, >10), location (lung, bone, or other) and whether metastases were amenable to local treatment based on multimodality joint clinic discussion. Toxicities were documented using the US National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0. Histological response on the surgical specimen was assessed using Huvo’s necrosis grading, wherein good responders were defined as those with <10% viable cells [11].

Treatment characteristics recorded from electronic medical records (EMR) included markers of non-compliance (failure to complete protocol and failure to complete treatment within the planned period with 25% additional time to allow for justifiable reasons for non-compliance), prior inadvertent treatment by peripheral practitioners, and febrile neutropenia as a marker of chemosensitivity.

The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki (Fortaleza, Brazil 2013), ICH-GCP, European Directive 2001/20/EC, US Code of Federal Regulations, South African Good Clinical Practice Guidelines, and other institutional regulatory requirements. Data collection and analyses were conducted in a single institution. This study is registered with Clinical Trials Registry—India (CTRI) identifier: CTRI/2023/10/059247.

Statistical Analysis:

Data was analysed using IBM SPSS version 25 Inc, Chicago, IL and RStudio software version 2023.03.0. Descriptive statistics were represented as median or percentages. T-tests or linear regression models were used to analyse continuous measures and chi-square tests, tests of proportions and logistic regressions were
used to analyse binary data. Survival was estimated using Kaplan-Meier method and compared using a log-rank test. The primary outcome was event-free survival (EFS). Secondary outcomes were overall survival (OS) and histological necrosis. Effect of covariates on survival were estimated using Cox proportional hazards analysis. Significant factors on univariate analysis were tested in multivariate analysis.

**Generation of the derivation and validation cohorts and identification of prognostic factors in the derivation cohort**

The whole cohort was divided in a 2:1 ratio into a derivation and validation cohort in a randomized fashion. Univariable Cox regression analyses identified factors prognostic for EFS in the derivation cohort. Factors with \( p < 0.05 \) on univariable analyses were included for multivariable analysis in a backward stepwise fashion based on likelihood ratio. Factors with \( p < 0.05 \) in the final multivariable model in the derivation cohort were used to formulate the risk score.

**Formulation of risk score**

A weighted score was provided to each prognostic variable. The score was computed based on the approximate ratios of the beta coefficients of each factor in the multivariable model. The total score was calculated by summation of individual prognostic factor scores and was used to divide patients into three clinically discriminatory risk groups.

**Validation of the risk score**

The risk score was validated by applying it separately to the derivation, validation, and whole cohorts separately. Kaplan Meier curves were constructed to represent EFS and OS in the three risk groups in each of the three cohorts. Harrell’s concordance index (c-index) was calculated for estimating the predictive ability of the risk category model for EFS and OS in the derivation, validation and whole cohorts. A receiver operating characteristic (ROC) curve was also constructed by comparing the predicted and actual 18-month and 36-month EFS and OS in each of the three cohorts and the timed area under the ROC curve (timed AUC) for the derivation, validation and whole cohort was estimated.

**Results:**

**Baseline Characteristics:**

There were 1103 AYA with OGS registered during the study period, of whom 748 (67.8%) were extremity osteosarcomas uniformly treated with the “OGS-12” protocol as first-line therapy, consisting of NACT, surgery and ACT. (Figure 1) Of these, 606 (81.0%) had non-metastatic disease. There were 263 non-metastatic ES, of whom 104 (39.5%) had extremity tumours treated with the “EFT-2001” protocol. Among 218 AYA with metastatic ES, 82 (37.6%) received the “EFT-2001” protocol, of whom (46.3%) had extremity tumours while the rest (chest wall, pelvis or other non-appendicular primary) were not included in this analysis as prespecified. Baseline characteristics are detailed in Table 1 and Table 2.

**Treatment Compliance, Protocol Completion and Prior Inadvertent Treatment:**

561 (92.6%) non-metastatic OGS were treatment-naïve at presentation, of whom 481 (85.7%) completed the entire treatment protocol consisting of NACT followed by surgery and ACT. Median total treatment duration was 27 (21-85) weeks. Of metastatic OGS, 83 (58.4%) patients completed the entire treatment protocol inclusive of NACT, Surgery and ACT, while 15 (10.5%) had received prior treatment.

Among non-metastatic ES, 91 (87.5%) were treatment-naïve at presentation, 79 (75.9%) underwent surgery after NACT, and 70 (67.3%) completed the treatment protocol.

**Histological Necrosis:**

Of 481 non-metastatic and 111 metastatic OGS patients analysable for histological response, there were 284 (59.0%) and 55 (49.5%) good responders respectively pathological complete response (100% necrosis). For metastatic ES, 10 (45.5%) patients had good histological response with 5 (22.7%) attaining 100% necrosis.
Compliance:

Of 1566 registered AYA with bone sarcomas, 182 (11.6%) defaulted after diagnosis. Among the treatment naive cohorts enrolled respectively on the “OGS-12” and “EFT-2001” protocols, 42 (6.1%) osteosarcoma and 18 (14.2%) Ewing’s sarcoma abandoned treatment subsequently. Overall, 379/481 (78.8%) non-metastatic OGS and 51/70 (72.8%) non-metastatic ES treated per-protocol were compliant to treatment.

Chemotoxicity:

264 (43.5%) non-metastatic OGS, 53 (37.3%) metastatic OGS, 54 (51.9%) non-metastatic ES and 16 (42.1%) metastatic ES cases had febrile neutropenia, with 121 (19.9%) non-metastatic OGS, 48 (33.8%) metastatic OGS, 24 (23.1%) non-metastatic ES and 14 (36.8%) metastatic ES requiring dose modification of at least one drug, respectively.

Outcomes:

For non-metastatic OGS, at a median follow-up of 59.7 (95% confidence interval (CI): 54.4-63.3) months, 5-year event free survival (5-EFS) was 54.8 (CI: 50.5-59.4)%, and 5-year overall survival (5-OS) was 72.7 (CI: 68.7-77.0)%. For metastatic OGS, 5-EFS was 18.7 (CI: 12.7-27.5)%.

For non-metastatic and metastatic ES, 5-EFS were 68.8 (CI: 59.5-79.5)% and 21.9% (CI 11.4-42.0)%.

Prognostic Factors

OGS:

For non-metastatic OGS, factors found significant on univariate analysis are shown in Table 3. On multivariable analysis, higher baseline SAP, neurovascular bundle involvement, joint involvement, poor histological necrosis, failure to complete treatment, prior treatment independently predicted inferior EFS.

In the metastatic cohort, failure to complete treatment protocol, poor histological necrosis, tumours not amenable to local treatment and >10 metastases were also predictive of superior EFS on multivariable analysis. (Table 4)

ES:

On multivariable analysis, failure to complete treatment protocol, prior treatment, residual viable tumor and tumor size >8cm were independent predictors for inferior EFS for non-metastatic tumours. (Table 5)

In the metastatic cohort, failure to complete protocol and tumours not amenable to local treatment independently predicted inferior EFS. (Table 6)

Model:

Non-Metastatic Osteosarcoma:

Variables included in the model for the whole cohort included failure to complete protocol (8.7 points), prior treatment (10.0 points), necrosis <90%: 4.3 points, neurovascular bundle involvement: 4.4 points, joint involvement: 6.3 points and SAP > median (204 U/l): 5.2 points (Table 7). In the validation cohort (n=158), factors that emerged significant and included in the final model were failure to complete protocol (7.1 points), prior treatment (10.0 points), necrosis <90%: 2.9 points, joint involvement: 5.1 points and SAP > median (204 U/l): 3.0 points (Table 8). Stratification was done by summation of the individual scores as follows; low risk (score <3), intermediate risk (3 - 8) and high risk (>8). Kaplan-Meier curves for EFS for the derivation (n=342), validation (n=158) and whole (n=600) cohort are depicted in Figure 2A[i], 2A[ii] and 2A[iii]. The c-index for whole, derivation and validation data are were 0.659, 0.664 and 0.651 respectively.

Non-Metastatic Ewing’s Sarcoma:

Factors significant in the cohort and included the final model were failure to complete protocol (4.8 points), prior treatment (8.5 points), necrosis <100% (10.0 points), and tumor size >8cm (4.5 points), depicted in the nomogram. (Figure 2B).
Metastatic Osteosarcoma

Factors significant in the cohort and included the final model were failure to complete protocol (10.0 points), in-amenability to local treatment (1.8 points), necrosis <90% (4.1 points), and >10 metastases (5.4 points), depicted in the nomogram (Figure 2C).

Metastatic Ewing’s Sarcoma

Factors significant in the cohort and included the final model were failure to complete protocol (5.7 points) and not being amenable to local treatment (10 points), depicted in the nomogram. (Figure 2D)

Discussion:

In this study, we analyzed a retrospective cohort of AYA with osteosarcoma treated at our center using a uniform non-HDMTX-based protocol “OGS-12”, and Ewing’s sarcoma treated with our institutional standard “EFT-2001” protocol. We formulated and validated prognostic scores separately for metastatic and non-metastatic osteosarcoma and Ewing’s sarcoma based on baseline clinical factors and tailored to a unique population of patients treated in a resource constrained setting with our in-house, low-cost, institutional standard protocols which have previously demonstrated survival outcomes are comparable to those published from Western countries [12-15].

For non-metastatic AYA sarcomas, features of high tumor burden including higher baseline SAP, neurovascular bundle involvement and joint involvement predicted poor EFS. This is consistent with published literature - serum alkaline phosphatase and lactate dehydrogenase are surrogates of osteoblastic activity and thus, elevated levels may indicate increased disease aggressiveness [16]. Additionally, vascular involvement noted radiologically in pretreatment MRI has been found independently to be an risk factor for OS and EFS in patients with Enneking IIB primary osteosarcoma involving extremities. [17] Poor histological necrosis also predicted inferior EFS, which is well described in existing literature.

Importantly, failure to complete treatment and prior treatment independently predicted inferior EFS. This is particularly significant in LMIC, with high treatment abandonment rates as well as failure to complete treatment protocol due to various issues including financial challenges, lack of education and motivation for treatment and logistic issues relating to the need to travel long distances and stay far from the patient’s hometown for the duration of treatment due to unavailability of cancer care near the place of residences. Thus, prompt referral to dedicated centres specializing in cancer care and awareness of primary health care physicians to recognize bone sarcomas and avoid inadvertent inappropriate medical or surgical intervention is of paramount importance.

For Ewing’s sarcoma, tumor size >8cm was an additional prognostic factor, consistent with reported literature. [18-19] In the metastatic cohort, failure to complete treatment protocol, poor histological necrosis, tumours not amenable to local treatment and >10 metastases were also predictive of superior EFS on multivariable analysis. determinants of survival. This underscores the importance of multimodality clinics to identify tumors amenable to curative treatment and avoid overtreatment for patients with extensive disease. It has been previously observed that osteosarcoma presenting only with lung metastases have better survival outcomes than metastases at other sites [20].

The factors that emerged prognostically significant for our patients were similar to those described in data from centres using HDMTX-based protocols, indicating the wide applicability of our results. For non-HDMTX regimens, particularly prevalent in LMICs, data on prognostic factors are scarce with only few observational studies [21-23]. Histologic response to chemotherapy has been uniformly reported to be a predictive factor in these studies. A study from Brazil has additionally reported presence of metastases at baseline, primary tumor site and type of surgery (amputation vs. limb sparing) as prognostically significant [24]. Nevertheless, the lacunae for studies specifically targeting bone sarcomas in LMICs remains apparent. Smaller sample sizes of existing studies, observational nature, and non-uniformity of treatment protocols makes generalizability of these results challenging. A potential strategy to overcome these shortcomings include
collaborative efforts with multi-institution studies to enhance understanding of osteosarcoma in LMICs. Importantly, several existing studies have included patients with both non-metastatic and metastatic tumors, with widely differing outcomes. We have addressed this limitation by separately analyzed homogenously treated populations of metastatic and non-metastatic osteosarcoma and Ewing’s sarcoma.

In our study, we developed separate prognostic models for non-metastatic and metastatic osteosarcoma and Ewing’s sarcoma based on the prognostic factors identified. We validated the risk score for non-metastatic osteosarcoma, and demonstrated effective discriminative ability for event-free survival between the three risk groups. For the other cohorts (metastatic osteosarcoma, and non-metastatic and metastatic Ewing’s sarcoma), we developed prognostic models depicted as nomograms, although validation could not be separately performed due to the limited sample size. Available prognostic models for risk stratification in osteosarcoma involve variable treatment modalities, clinician preferences, surgical expertise and chemotherapy protocols which precludes generalizability of these models. [25-28]. For Ewing’s sarcoma, existing models have largely utilized treatment-related factors such choice of local treatment, factors that vary in different centres due to individual clinician preference and expertise. [29-34] In developing our prognostic models, we have analyzed homogenously treated cohorts and reinforced the importance of baseline indicators of tumor aggressiveness, chemosensitivity as indicated by histologic response to chemotherapy, and general treatment-related factors unique to patients in LMIC settings, such as failure to complete treatment protocol and prior inadvertent treatment before referral to advanced oncology centres.

The prognostic models we report are important and unique as they are derived from a prospective analysis of homogenously treated AYA in a LMIC setting. The specific challenges faced by this vulnerable subset of patients has been stressed upon. The wide implications of our results include healthcare policy-making, in the context of need for early identification by appropriate awareness and training of primary care physicians and timely referral to sarcoma reference centres, and the importance of strategies to improve protocol completion by efforts such as targeted nutritional intervention, extended growth factor support and patient navigation facilities. Risk stratification of patients aids selection of patients who would benefit from aggressive treatment as well as those who may achieve comparable outcomes with less aggressive modalities with improved quality of life. Traditionally, escalation of treatment for patients with high-risk disease has been based on histologic response after completion of neoadjuvant chemotherapy [35-36]. Use of other important prognostic factors as described in our study may be used to identify patients who may benefit from a less intensive approach such as metronomic chemotherapy regimens and early incorporation of palliative care, particularly in resource-constrained settings [37-38].

The prognostic implication of common social challenges have been highlighted, including prior inadvertent treatment and the importance of compliance in the form of protocol completion. We did not analyze socioeconomic strata due to unavailability of uniform data, however, surrogate parameters including compliance as assessed by treatment duration and protocol completion, as well as prior inadvertent treatment were analyzed. Importantly, majority of our patients are constrained financially and socially and depend on financial aid from various government schemes for cancer treatment. Another study from India has evaluated location of primary residence of the patient and the distance of the residence from the hospital and not found prognostic significance for osteosarcoma [23].

**Strengths and Limitations:**

This is the largest, single-centre prospective analysis of prognostic factors for AYA with bone sarcomas globally, with the first prognostic model tailored for AYA with generalizable results for LMIC.

Limitations include the shorter follow-up and lower number of AYA with Ewing’s sarcoma, which is as expected for a rare cancer. Additionally, the prognostic scores for metastatic osteosarcoma, and for both non-metastatic and metastatic osteosarcoma could not be validated in a separation validation cohort due to lower sample sizes. Socioeconomic backgrounds of our patients were not assessed with objective scales such as the Kuppuswamy scale; however, surrogate parameters such as treatment duration as an indicator for compliance, prior inadvertent treatment and protocol completion were included in the analysis.
Conclusion:

We conclude that simple prognostic models predict the prognosis in individual homogenous cohorts of adolescent and young adult patients with non-metastatic and metastatic osteosarcoma and Ewing’s sarcomas. In addition to conventional prognosticators, failure to complete the treatment protocol (all cohorts) and the disease not being amenable to curative treatment (metastatic cohort) were associated with inferior outcomes. These simple prognostic models are effective and with wide applicability including in LMIC and merit appropriate recognition.

Acknowledgements

We thank Ms Priyanka Patil, Ms Sushama Gavit and our team of trial coordinators for their valuable efforts in telephonically following up our patients, and the entire Bone and Soft Tissues (BST) disease management group (DMG) and the Department of Medical Oncology, Tata Memorial Hospital, Mumbai, for all their inputs during clinical decision-making in various cases. We would also like to express our gratitude towards our patients and their caregivers.

References


LEGENDS:

Figure 1: Figure 1 is a CONSORT diagram depicting the number of patients analyzed in the current study

Figure 2A[i]: Figure 2A[i] is a Kaplan-Meier curve depicting event-free survival for the patients with non-metastatic osteosarcoma: derivation cohort (n=342)

Figure 2A[ii]: Figure 2A[ii] is a Kaplan-Meier curve depicting event-free survival for the patients with non-metastatic osteosarcoma: derivation cohort (n=158)

Figure 2A[iii]: Figure 2A[iii] is a Kaplan-Meier curve depicting event-free survival for the patients with non-metastatic osteosarcoma: derivation cohort (n=500)

Figure 2B: Figure 2B is a nomogram depicting the prognostic model for non-metastatic Ewing’s Sarcoma

Figure 2C: Figure 2C is a nomogram depicting the prognostic model for metastatic osteosarcoma

Figure 2D: Figure 2D is a nomogram depicting the prognostic model for metastatic Ewing’s Sarcoma

Hosted file


Hosted file