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Title: Pathologic Fractures As Prognostic Factors For Survival, Local Recurrence And Distant Metastases In Osteosarcoma Of The Extremities

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Background: Consensus has not been reached in establishing pathologic fractures at presentation in patients with osteosarcoma as a predictor of local recurrence, increased distant metastases and decreased survival. It is not known how histologic features and grade of osteosarcoma are associated with higher pathologic fracture rates. We believe that a more aggressive biology of the tumor is associated with a higher pathologic fracture rate. Therefore, higher local recurrence and lower survival maybe consequences of a more aggressive biology and not the fracture per se.

Question: Our objective in this study is to determine how histological aggressiveness and biological behavior in osteosarcoma are predictive of pathologic fractures, higher local recurrence, higher rate of distant metastases and poorer survival.

Methods: The population of this retrospective multi-centered study consisted of 392 patients with osteosarcoma of the extremities provided by 3 institutions. All patients were treated in a standard fashion with surgery and pre and post surgical chemotherapy. Patients were excluded if (1) they underwent oncologic resection of the osteosarcoma at an outside institute or (2) they were diagnosed with an extraskeletal osteosarcoma. We collected data on demographics; pre, peri and postoperative factors and treatments; and histological features of the tumor (i.e. grade and subtype). Predictors with a p-value of <0.05 in bivariate analysis (Cox proportional hazards regression), were put in a multivariable model predicting local recurrence, distant metastases.

Results: Of the 392 patients in this study, 70 presented with a pathologic fracture and 59 presented with distant metastases. After surgical treatment 35 developed a local recurrence, 86 developed distant metastases and 94 died. In multivariable analysis presence of a pathologic fracture (Hazard Ratio: 2.42, 95%CI: 1.39 – 4.19, P = 0.002), age (Hazard Ratio: 1.03, 95%CI: 1.02 – 1.04, P < 0.001), amputation (Hazard

Ratio: 3.07, 95%CI: 1.69 – 5.60, $P < 0.001$), and metastatic disease at presentation (Hazard Ratio: 6.18, 95%CI: 3.43 – 11.1, $P < 0.001$) were significant predictors for death. Predictors for local recurrence included metastatic disease at presentation (Hazard Ratio: 2.60, 95%CI: 1.09 – 6.18, $P = 0.031$) and post-operative radiotherapy (Hazard Ratio: 4.62, 95%CI: 1.72 – 12.4, $P = 0.002$). For distant metastases post-operative radiotherapy (Hazard Ratio: 2.66, 95% CI: 1.23 – 5.79, $P = 0.013$), tumor volume (Hazard Ratio: 1.25, 95% CI: 1.04 – 1.51, $P = 0.018$) and a high grade tumor (Hazard Ratio: 2.10, 95% CI: 1.04 – 54.27, $P = 0.039$) were significant predictors.

Conclusion: This study suggests that the presence of a pathologic fracture is predictive for a worse survival and a high grade tumor is predictive for distant metastases. Detailed histologic information of the tumors is needed to determine whether the pathologic fracture itself or the type of tumor is the primary cause for the influence on survival rate, local recurrence and distant metastases.

Level of evidence: 3