

**Title**

The effect of surgical timing on the outcome of localized extremity osteosarcoma

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## **ABSTRACT**

**Background:** Initially, the rationale for neoadjuvant chemotherapy was devised owing to the development of limb-salvaging procedures. Originally, limb-salvage endoprostheses were custom made and took several weeks–months to manufacture, and neoadjuvant therapy was employed to bridge the gap between biopsy and resection. Since several trials that incorporated pre-surgical chemotherapy resulted in improved outcomes for patients, neoadjuvant chemotherapy has been recommended for osteosarcoma patients.

However, there are several proposed disadvantages of delayed tumor removal which include a high initial tumor burden is not optimal for first-order chemotherapy kinetics, an increased probability of facilitating the selection of drug-resistant cells in the primary tumor, a delay in the definitive control of bulk disease.

**Purpose:** To evaluate the effect of the timing of surgery on the outcome of localized osteosarcoma, we performed this retrospective non-randomized cohort study. We divide our patient into two distinct group, namely immediate surgery group and delayed definitive surgery group and analyzed the prognostic factors for survival in our cohort.

**Material and Method:** The records of 315 localized extremity osteosarcoma patients treated between Jan. 2005 and Jun. 2014 at our institute were retrospectively reviewed.

A total of 51 patients were excluded for the following reasons: follow-up was less than 2 years (49 patients), data for preoperative volume were unavailable (2 patients).

The independent factors assessed were age, gender, primary tumor location, pathologic subtype, tumor volume at presentation, type of operation, surgical margin and surgery timing. For survival analysis, the end point used were time to metastasis. Metastasis-free survival was measured from the date of diagnosis to the time of metastatic event.

Patients who did not experience a metastatic event were assessed at final follow-up.

Fisher's exact chi square test and the Student's t-test were used to identify differences between immediate surgery group and delayed surgery group.

The Kaplan-Meier method and the log-rank test were used to identify survival differences. Multivariate analysis by Cox proportional hazard model was performed with all factors that showed statistical significance in univariate analysis. Analyses were performed using SPSS1 Version 13.0 (SPSS Inc, Chicago, IL, USA), and p values less than 0.05 were considered significant.

**Results:** Among 265 eligible patients, 70 patients received immediate surgery. There were 167 males and 98 female patients with mean age of 20.7 (3-78). Six patients underwent amputation and 28 (10.5%) patients developed local recurrence. In immediate surgery group, no patient received amputation. However, this group showed

a significant higher proportion of patients with age over 40 ( $P < 0.001$ ). The local recurrence rate was not significantly different between two groups (9.7% for delayed surgery group vs 12.9% for immediate surgery group,  $P = 0.499$ )

In the cohort study, univariate survival analysis on the 265 study patients revealed that preoperative tumor volume ( $P = 0.003$ ), surgical margin ( $P < 0.001$ ) and local recurrence ( $P < 0.001$ ) were negatively related to metastasis-free survival. Age over 40 was negatively related to metastasis-free survival with a marginal statistical significance ( $P = 0.058$ ). Although delayed surgery group showed better survival compare to the immediate surgery group (63.4% vs 55.1%), it did not reach the statistical significance ( $P = 0.175$ ).

Multivariate analysis revealed that preoperative tumor volume ( $P = 0.012$ ), surgical margin ( $P = 0.015$ ) and local recurrence ( $P < 0.001$ ) independently predicted reduced metastasis-free survival.

**Conclusion:** There was no statistically significant advantage in metastasis-free survival for the patients given neoadjuvant chemotherapy.