CHEMOTHERAPY-SURGERY INTERVAL EFFECTS ON TUMOR NECROSIS AND OUTCOME IN CHILDREN AND YOUNG ADULTS WITH OSTEOSARCOMA

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Abstract

Background/Objective: Osteosarcoma treatment incorporates chemotherapy and surgery. Resection of the primary tumor usually occurs after induction chemotherapy. Occasionally, scheduling challenges and medical complications result in delay. The goal of this study is to determine if an increased interval between completion of neoadjuvant therapy and surgical resection correlates with decreased tumor necrosis and inferior outcomes in children and young adults with osteosarcoma. **Design/Method:** We conducted a retrospective chart review of 121 patients age less than 40 years diagnosed with osteosarcoma treated at a single tertiary medical center between 2000-2022. Inclusion criteria included receipt of two cycles of neoadjuvant methotrexate, cisplatin, and doxorubicin. Association of the interval from completion of induction chemotherapy to resection with tumor necrosis (Spearman's correlation) and outcomes (multivariable Cox hazard regression) were analyzed. **Results:** There was no significant correlation between interval length and tumor necrosis. However, patients with an interval greater than 16 days had lower 5-year event free survival (p=0.019). Multivariable adjusted analysis of patients with initially localized disease revealed that each day increase in interval length corresponds with a 1.1 times greater hazard of having an event (95% CI: 1.02 to 1.19; p=0.016). **Conclusion:** Delays in local control were not associated with tumor necrosis. This is consistent with the hypothesis that tumor necrosis is a biologic marker of a tumor's sensitivity to chemotherapy and may not be affected by minor regimen aberrations. However, surgical delay from completion of induction chemotherapy may confer worse outcomes. Longer intervals generally confer worse outcomes in patients with initially localized disease.

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Abbreviations

EFS	Event free survival
OS	Osteosarcoma
MAP	Methotrexate, Adriamycin (doxorubicin), cisplatin
HR	Hazards-ratio
SOC	Standard of care
LC	Local control
MIOS	Multi Institutional Osteosarcoma Study
MAPIE	Methotrexate, Adriamycin (doxorubicin), cisplatin, ifosfamide, etoposide

ABSTRACT

Background/Objective: Osteosarcoma treatment incorporates chemotherapy and surgery. Resection of the primary tumor usually occurs after induction chemotherapy. Occasionally, scheduling challenges and medical complications result in delay. The goal of this study is to determine if an increased interval between completion of neoadjuvant therapy and surgical resection correlates with decreased tumor necrosis and inferior outcomes in children and young adults with osteosarcoma.**Design/Method:** We conducted a retrospective chart review of 121 patients age less than 40 years diagnosed with osteosarcoma treated at a single tertiary medical center between 2000-2022. Inclusion criteria included receipt of two cycles of neoadjuvant methotrexate, cisplatin, and doxorubicin. Association of the interval from completion of induction chemotherapy to resection with tumor necrosis (Spearman's correlation) and outcomes (multivariable Cox hazard regression) were analyzed.**Results:** There was no significant correlation between interval length and tumor necrosis. However, patients with an interval greater than 16 days had lower 5-year event free survival

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MAIN TEXT

Introduction

Osteosarcoma (OS) is the most common primary bone malignancy, representing 3 to 5% of childhood cancers.[1–3] OS has a bimodal distribution, with the majority of cases occurring in adolescents and another peak occurring in late adulthood.[4,5] OS is highly aggressive, with 15-30% of patients presenting with metastatic disease at the time of diagnosis, most commonly to the lungs. Monotherapy with surgery is rarely sufficient for cure, as greater than 80% of patients develop distant metastatic disease when treated with surgery alone .[6,7] The Multi Institutional Osteosarcoma Study (MIOS) conducted from 1982 to 1984 demonstrated significant increases in 6-year survival rates for patients treated with surgery and chemotherapy compared to surgery alone, highlighting the importance of combined multimodal treatment.[8] However, since initial treatment advances in the 1970s and 1980s, survival rates have largely plateaued, with a 5-year event-free survival of approximately 70% in patients with localized disease and 20% in patients with metastatic disease at the time of diagnosis.[9–11]Current standard of care (SOC) treatment for patients with osteosarcoma includes surgical resection of all sites of disease, when feasible, in addition to systemic chemotherapy. The most established chemotherapeutic regimen incorporates methotrexate, Adriamycin (doxorubicin), and platinum (cisplatin) (MAP), which has demonstrated the best outcomes to date.[12–16] Frequently, two cycles of neoadjuvant MAP are administered prior to surgical resection of the primary tumor (Figure 1). Local control (LC), which in most instances consists of surgery, ideally occurs soon after completion of neoadjuvant chemotherapy; however, scheduling challenges and therapy complications can result in delay. After recovery from surgery, patients typically receive an additional four cycles of MAP chemotherapy. In patients with pulmonary metastatic disease, metastasectomy is recommended. Tumor necrosis, calculated by pathologists by analyzing the surgically resected tumor specimen and quantifying the percentage of cells that have become necrotic, is a strong prognostic factor in osteosarcoma.[17] Although a continuous variable, several clinical trials defined patients having a good response as having less than 10% of viable tumor remaining (corresponding to 90% tumor necrosis). Patients who do not meet this criterion are referred to as poor responders (less than 90% tumor necrosis) which confers a worse outcome.[18]Delays greater than 21 days in starting adjuvant chemotherapy have previously been shown to be associated with decreased overall survival in a retrospective analysis, but information is lacking regarding the interval between neoadjuvant chemotherapy completion and surgery.[19] The goal of this study was to determine if the time from completion of neoadjuvant chemotherapy to surgical resection has implications on tumor necrosis or outcomes in children and young adults with osteosarcoma.

Methods

Following institutional review board approval, a comprehensive chart review of patients treated for osteosarcoma at Monroe Carell Junior Children's Hospital at Vanderbilt and Vanderbilt University Medical Center between 2000 and 2022 was performed. Follow up data was obtained until December 2023. Patients who were treated medically at outside institutions were included and data was obtained through review of outside records. Patients with unresectable disease, unclear neoadjuvant regimen, or inadequate information

for analysis were excluded from the study. Inclusion criteria included the diagnosis of osteosarcoma as confirmed by pathologic evaluation and surgical resection performed at Vanderbilt. Additional inclusion criteria included completion of two cycles of neoadjuvant MAP regimen (defined by two courses of cisplatin and doxorubicin and at least two but no more than six doses of methotrexate), and age less than 40 years. Demographic and clinical data collected include age at diagnosis, sex, histologic classification, grade, site of tumor, location in long bone (if applicable), stage, year of chemotherapy initiation, number of neoadjuvant methotrexate doses given, margin status at time of surgery, type of event (if applicable) after the completion of chemotherapy, event-free-survival (EFS), and duration of follow-up. Metastatic disease at the time of diagnosis was defined as a patient having one pulmonary nodule greater than one centimeter, greater than two pulmonary nodules equal to or larger than five millimeters, or distant metastasis identified on initial staging workup. The interval from completion of adjuvant therapy to surgery was defined as the duration between the date of completion of the last methotrexate dose to the date of surgical resection. EFS was calculated as the duration from the date of completion of initial therapy until the date of an event, including recurrent localized disease, new or relapsed metastatic disease, or death. Patients with refractory disease who did not achieve remission were defined as having an EFS of zero days. In the cases of disease relapse, the date of the event was defined as the date when the relapse was confirmed via biopsy and pathologic review. If a biopsy was not obtained, the event was defined as the date of radiologic confirmation.

Statistical Analysis

All statistical analysis was conducted in R (R Core Team) and an alpha value of 0.05 was set as a threshold for statistical significance. A Spearman's correlation analysis was utilized to analyze the correlation between neoadjuvant therapy completion to surgery interval length and tumor necrosis at the time of surgery. Kaplan Meier analyses were performed on those with an interval greater than versus less than or equal to 14, 15, 16, and 17 days. A multivariable Cox hazards regression for EFS and a linear regression for tumor necrosis were additionally performed, treating interval as a continuous variable with a linear effect, and controlling for age at diagnosis, margin status, tumor site, histologic subtype, and stage at diagnosis as potential confounders. Collapsed categories were used for tumor site and histologic subtype. A post-hoc multivariable Cox hazards regression was performed on patients with localized disease at the time of diagnosis, controlling for age at diagnosis, margin status, tumor site, and histologic subtype. A forest plot of hazard ratios (HR) was created for both multivariable Cox model analyses.

Results

Patient characteristics

One hundred twenty-one patients were included in the initial database review (Figure 2). Of these, 92 patients met inclusion criteria. Exclusion justification included patients that received more than two neoadjuvant chemotherapy cycles (N=15) or less (N=3). Two patients had surgical resection prior to initiation of chemotherapy and three had no surgical resection performed. An additional six patients received a neoadjuvant regimen other than MAP. In addition to the 29 patients who did not meet inclusion criteria, seven patients did not have adequate medical records, resulting in 85 patients included in the final analysis. Demographic data is shown in Table 1. The median age was 13.9 years. Thirteen (15.3%) had metastatic disease at the time of diagnosis. Fifty-one patients (60.0%) had an osteoblastic subtype, with the second most common subtype being chondroblastic (N=17, 20.0%). Forty-two (49.4%) patients had a femur primary, followed by tibia (N=20, 23.5%). Eighty (94.1%) of patients received the expected four doses of neoadjuvant methotrexate; 3 (3.5%) patients received less than four doses and two (2.4%) patients received more than four doses. Ten (11.8%) patients had positive resection margins at the time of LC. The median interval length was 16 days. Demographic and clinical information was also divided into those with intervals greater than 14 days (51 patients, 60.0%) and less than or equal to 14 days (34 patients, 40.0%). Percentage of

patients with metastatic disease was 13.7% and 17.6% respectively.

Tumor Necrosis

There is weak correlation between the interval of last methotrexate dose to surgery and tumor necrosis (rho = -0.18 p = 0.096) (Figure 3) with a trend that longer interval lengths correlate with decreased tumor necrosis. However, there is significant variability in the data, and this relationship is not statistically significant. In multivariable linear regression analysis, each additional day of interval length corresponds to a 1.1% decrease in tumor necrosis among patients with the same age at diagnosis, tumor site, histological subtype, stage, and year of diagnosis, though this estimate does not reach statistical significance with a 95% confidence interval (CI) of a 2.3% decrease to a 0.1% increase (Supplemental Table 1).

Event Free Survival

An interval length of greater than 16 days demonstrated lower 5-year EFS than less than or equal to 16 days (p = 0.019, Figure 4C). Similarly, interval length greater than 17 days corresponded to lower 5-year EFS than less than or equal to 17 days (p = 0.014, Figure 4D). There was no statistically significant difference in 5-year EFS for patients with an interval greater than 14 days versus less than or equal to 14 days or patients with an interval greater than 15 days versus less than or equal to 15 days, although similar trends were observed (Figure 4A and 4B respectively). However, in a multivariable Cox model adjusting for relevant confounders, each additional day of interval length did not correspond to increased risk of an event in a statistically significant manner (HR = 1.04, 95% CI: 0.98 to 1.10; Figure 5A and 5B). Metastatic disease at the time of diagnosis and positive surgical resection margins were associated with an increased risk of having an event (HR = 6.8, p < 0.001; HR = 3.0, p = 0.024). When performing a subgroup analysis on patients with localized disease at the time of diagnosis, each day of increased interval length resulted in a 1.1 times greater hazard rate (95% CI: 1.02 to 1.19, p = 0.016) of having an event in patients with the same age at diagnosis, histological subtype, tumor site, and margin status at surgery (Figure 5C and 5D). This suggests that the cumulative impact of many days of delay could be substantial. Positive surgical resection margins also correlated with an increased hazard of having an event (HR = 3.5, p = 0.020).

Discussion

Osteosarcoma remains one of the most challenging pediatric cancers to treat. Despite therapy advancements in the 1970s to 1980s, survival rates have plateaued over the past four decades with a 5-year overall survival rates remaining around 63%.[9,10] Advancements continue to prove challenging, in part due to the rarity of the disease and very complicated biology. Tumor necrosis has long been known to be a strong prognostic factor, but its utility in informing changes in adjuvant regimens remains elusive. A large, international randomized controlled trial, EURAMOS-1, was conducted to investigate whether intensified MAP plus ifosfamide and etoposide (MAPIE) therapy in patients with poor response (tumor necrosis less than 90%) would result in improved outcome. They also investigated whether maintenance therapy with pegylated interferon alfa-2b in patients with good histologic response (tumor necrosis greater than or equal to 90%) was superior to MAP alone. These studies failed to demonstrate improvement in long-term outcomes when stratifying treatments based on histologic response.[12,13]The results from our study revealed that minor aberrations from the SOC schedule did not correlate with lower tumor necrosis. This is consistent with the hypothesis that tumor necrosis is likely a biologic marker of a specific tumor's sensitivity to chemotherapy and is thus not improved with small alterations of the existing neoadjuvant regimen. It should be noted, however, that in our patient population, all timing aberrations were relatively minor, with the longest neoadjuvant chemotherapy to surgery interval being 33 days. It is reasonable to hypothesize that longer delays could result in tumor regrowth, and thus a lower percentage of tumor necrosis. This study did, however, demonstrate that delays in LC may confer worse outcome, as defined by 5-year EFS. Additionally, longer neoadjuvant chemotherapy

to surgery intervals in general correlate with increased risk of having an event in patients with localized disease at the time of diagnosis after adjusting for relevant potential confounders. This is clinically intuitive, as patients with metastatic disease or very large primary tumors at the time of diagnosis face poor outcomes regardless of treatment. Though it is unclear if there is an optimal interval length between neoadjuvant treatment and surgery, this study suggests that attempts to reduce delays to surgery may improve outcomes in children and young adults with osteosarcoma. This requires early surgical planning, close communication with surgeons regarding treatment delays, and ample coordination with outside institutions when medical and surgical management is occurring at different locations. Notably, a recent study conducted at King Hussein Cancer Center in Jordan examining patients under the age of 18 with non-metastatic osteosarcoma demonstrated that a time from diagnosis to LC greater than or equal to 18 weeks was associated with worse event free survival and overall survival.[20] This is consistent with our findings that treatment delay generally is associated with worse outcomes. It is important to note that intervals from diagnosis to LC greater than 18 weeks are uncommon in our clinical setting. Only one patient had a time from the initiation of chemotherapy to LC interval greater than 18 weeks. While this does not include time from diagnosis to initiation of chemotherapy, delays prior to chemotherapy initiation are exceedingly uncommon. This study adds context that more minor delays, particularly after completion of neoadjuvant chemotherapy, also may confer worse outcomes. There are limitations to our retrospective study. It does not allow us to fully control covariate differences between the exposure and control groups, introducing a greater degree of potential confounders than a randomized clinical control study. This study can only suggest correlation, and the possibility of an unmeasured confounder, such as socioeconomic barriers contributing to treatment delays and contributing to worse outcomes, cannot be excluded. There are limitations to assessing current patient status based on accessibility of information. Attempts to mitigate this included obtaining follow up information from outside institutions, as is standard practice, when possible and censoring all follow up information at 5-years. Since OS is such a highly aggressive cancer, most patients who will relapse do so in the first five years following completion of chemotherapy. Notably some patients (2019-2022) do not yet have five years of follow up information and this is a limitation of this study. Additionally, though tumor necrosis is a universally established measurement for osteosarcoma, there may be a certain degree of variability in the exact measurements between pathologists. Another limitation of this study is the fairly small sample size; results such as the correlation between interval length and tumor necrosis were not statistically significant but may require more data to yield sufficient precision before meaningful correlations can be ruled out. However, this is a substantial sample size for a rare disease like OS. Relatedly, interval length was treated as a linear effect in all models due to limited modeling degrees of freedom but may have a non-linear effect on EFS. Finally, it is important to note that we are reducing highly individualized chemotherapy and disease courses into measurable data. Many factors affect a patient's therapeutic course. While the neoadjuvant regimen largely remains unchanged, toxicities in the adjuvant setting may lead to non-optimal regimens, altering outcomes but not being captured in the data. In conclusion, our study demonstrates that delays in local control are not strongly associated with lower tumor necrosis. However, surgical delays from completion of induction chemotherapy correlate to worse outcome in localized disease. Therefore, minimizing the delay from the completion of neoadjuvant chemotherapy to LC should continue to be weighed against the potential risks of infection and wound healing complications associated with decreasing this interval.

Conflict of Interest Statement

SCB serves on a data safety committee for Merck and also serves as a scientific advisor for Roche Pharmaceuticals.

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Legends

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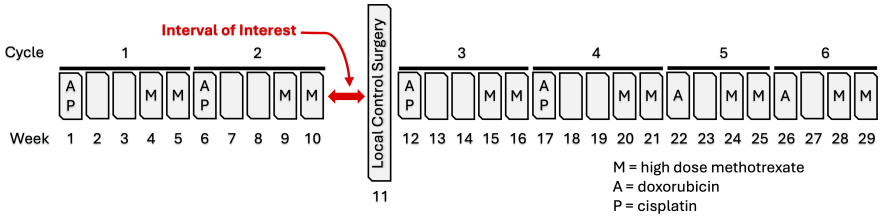
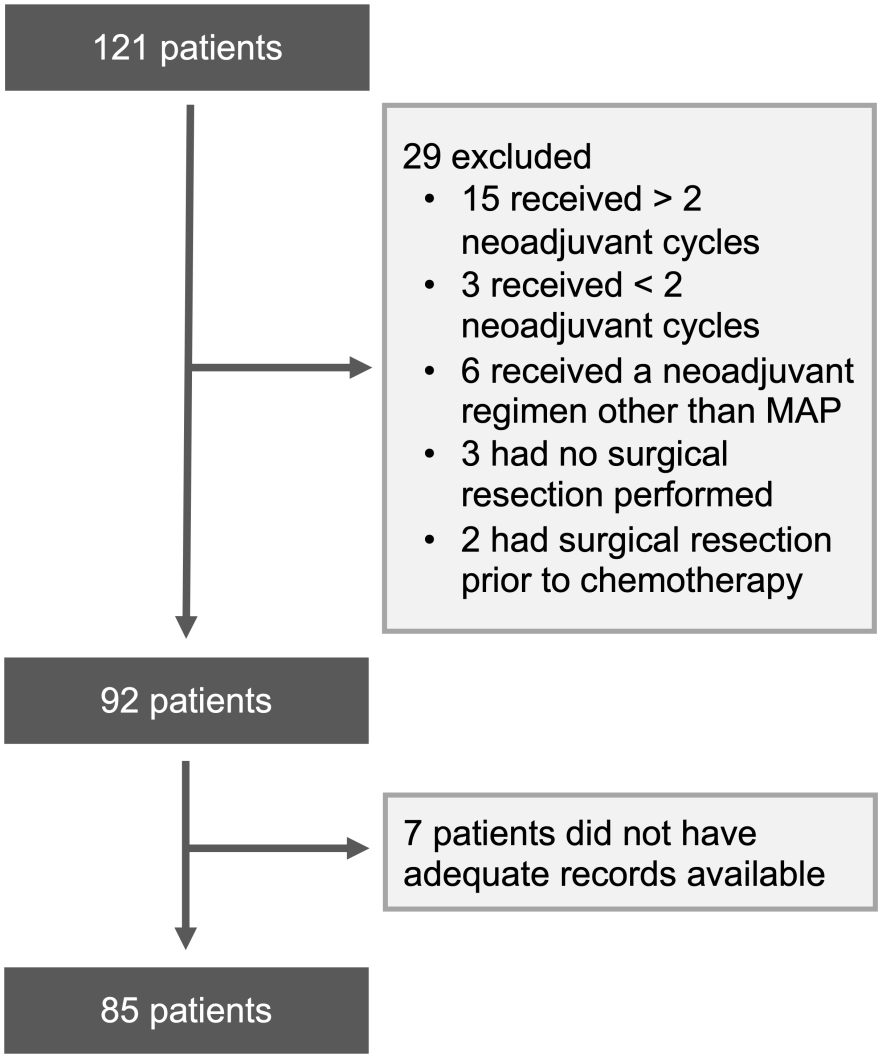
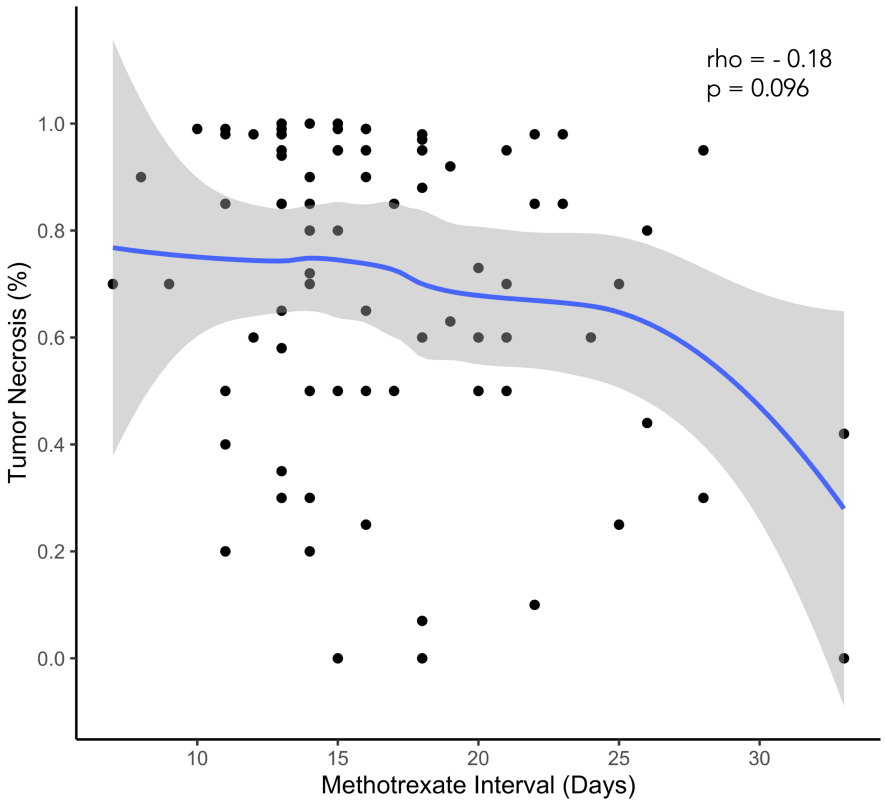
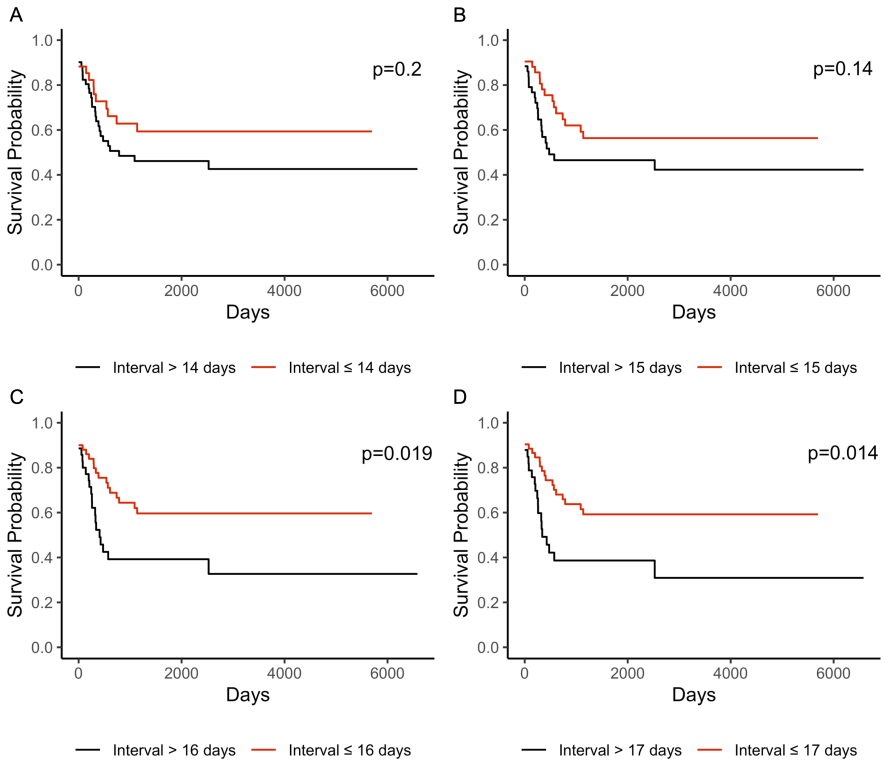
FIGURE 1 Schematic overview of the institutional standard of care treatment for children and young adults with osteosarcoma, highlighting end of neoadjuvant chemotherapy to surgery interval.

FIGURE 2 Flow diagram of participants.









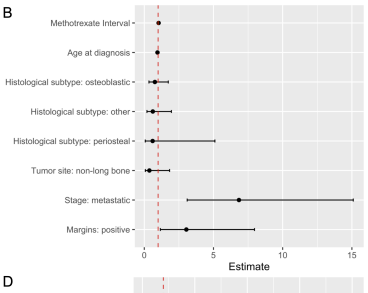
A

	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
Interval length	1.036	0.975	1.10	0.252
Age at diagnosis	0.954	0.874	1.04	0.300
Histology: osteoblastic	0.766	0.338	1.73	0.522
Histology: other	0.616	0.194	1.96	0.412
Histology: periosteal	0.603	0.071	5.10	0.642
Tumor site: non-long bone	0.369	0.075	1.83	0.222
Stage: metastatic	6.841	3.100	15.10	0.000
Margins: positive	3.039	1.160	7.96	0.024

C

	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
Interval length	1.102	1.018	1.19	0.016
Age at diagnosis	0.929	0.826	1.04	0.214
Histology: osteoblastic	1.082	0.395	2.96	0.878
Histology: other	0.476	0.109	2.08	0.324
Histology: periosteal	0.901	0.095	8.52	0.928
Tumor site: non-long bone	0.413	0.082	2.08	0.283
Margins: positive	3.501	1.220	10.05	0.020

B



D

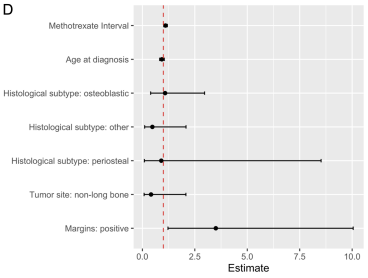


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Table 1_Demographics.docx available at https://authorea.com/users/826062/articles/1221398-chemotherapy-surgery-interval-effects-on-tumor-necrosis-and-outcome-in-children-and-young-adults-with-osteosarcoma