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Neoadjuvant chemotherapy and endoprosthetic reconstruction for lower extremity sarcomas: Does timing impact complication rates?

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Cover Letter: Young Investigator Award

I am currently a fourth-year orthopaedic surgery resident and will be undergoing a fellowship in musculoskeletal oncology at the University of Toronto in 2023-24. With respect to the current abstract, I was the lead author who conceived the idea, analyzed the data and wrote the abstract/manuscript.

Abstract

Background: Sarcoma patients undergoing surgical resection and endoprosthetic reconstruction often receive neoadjuvant chemotherapy (NACT). In other areas of surgical oncology, the optimal timing of neoadjuvant chemotherapy is an area of debate. However, the systemic effects of neoadjuvant chemotherapy may increase the risks of postoperative complications and surgical site infections (SSI) in orthopaedic oncology.

Purpose: The objectives of this study were to describe the current neoadjuvant chemotherapy practices in patients undergoing endoprosthetic reconstruction for primary bone and soft tissue sarcomas (STS) of the lower extremities, and to identify the impact of timing of neoadjuvant chemotherapy on postoperative SSIs and reoperation rates.

Methods: This was a secondary analysis of the recently completed *Prophylactic Antibiotic Regimens in Tumor Surgery* (PARITY) trial. Patients who underwent neoadjuvant chemotherapy, tumor resection and endoprosthetic reconstruction for a bone or soft tissue sarcoma were included. Based on the distribution of the data, the time interval from the last dose of cytotoxic chemotherapy to surgery (TTS) was categorized into 3 groups: <3 weeks, 3-6 weeks, and >6 weeks. Multivariate Cox proportional hazards regression models were created to evaluate the if NACT timing was predictive of SSI and reoperations.

Results: Of the 604 patients in the PARITY trial, 216 patients from 39 clinical sites underwent surgery for a primary bone or soft tissue sarcoma, received neoadjuvant chemotherapy as part of their care and had data available to analyze. The most common diagnosis was osteosarcoma (75%), followed by Ewing's sarcoma (16%). The median time from completion of neoadjuvant chemotherapy to surgery was 24 days (interquartile range 15, 42 days). The adjusted Cox proportional hazards model demonstrated that the timing of NACT did not impact SSI rates or reoperation rates (Table 1 and 2). Longer operative time was an independent predictor of both SSI (Hazards ratio [HR] per hour of 1.21 [95% 1.07, 1.40], p=0.002) and reoperation rates (HR of 1.15 per hour [95%CI 1.03, 1.28], p=0.014)

Conclusions: The timing of surgery following NACT varied considerably. Chemotherapy timing did not impact SSI or reoperations in patients undergoing surgical resection and endoprosthetic reconstruction in sarcoma patients. Future research is required to evaluate the impact of timing of NACT on long-term outcomes in this patient population.

Table 1. Cox proportional hazards model evaluating predictors of surgical site infection

		95% CI for HR		
	HR	Lower	Upper	P Value
Age (per year)	1.00	0.97	1.02	0.687
Location				
Femur (ref)				
Tibia	0.96	0.42	2.2	0.923
Diagnosis				
Bone Sarcoma (ref)				
Soft tissue Sarcoma	1.03	0.21	5.00	0.975
TTS				
<3 weeks				
3-6 weeks	1.78	0.80	3.96	0.156
>6 weeks	1.50	0.56	3.97	0.418
Preoperative Neutropenia ($<1500/mm^3$)	0.17	0.023	1.30	0.087
No (ref)				
Yes				
Soft tissue mass				
No (ref)				
Yes	2.03	0.47	8.8	0.344
Operative Time	1.21	1.07	1.40	**0.002**
HR: hazards ratio; CI: confidence interval; ref: reference; TTS: time to surgery; **bolded:** statistically significant ($p<0.05$)				

Table 2. Cox proportional hazards model evaluating predictors of reoperation.

	HR	95% CI for HR	P Value

		Lower	Upper	
Age (per year)	0.99	0.98	1.01	0.857
Location				
Femur (ref)				
Tibia	0.82	0.41	1.65	0.575
Diagnosis				
Bone Sarcoma (ref)				
Soft tissue Sarcoma	1.04	0.30	3.65	0.953
TTS				
<3 weeks (ref)				
3-6 weeks	1.02	0.54	1.92	0.958
>6 weeks	0.92	0.40	2.11	0.848
Preoperative Neutropenia ($<1500/mm^3$)				
No (ref)	0.45	0.16	1.31	0.454
Yes				
Soft tissue mass				
No (ref)				
Yes	1.70	0.59	4.9	0.326
Operative Time	1.15	1.03	1.28	**0.014**

HR: hazards ratio; CI: confidence interval; ref: reference; TTS: time to surgery; **bolded:** statistically significant ($p<0.05$)