Investigating Circulating Tumor DNA as a Biomarker for Patients with High-Grade Sarcoma

Maahir Patel
University of Wisconsin, Madison

Maahir Patel, Rohit Sharma, MD
Cancer Care Research Center

Background: Soft tissue sarcomas represent a heterogeneous and aggressive group of mesenchymal malignancies. For patients with localized, high-grade disease, neoadjuvant therapy (chemotherapy, immunotherapy, or both) is standard to facilitate radical surgical resection. Achieving a complete pathological response (CR), defined as the complete absence of viable tumor in the post-resection surgical specimen, is a critical surrogate endpoint. Currently, evaluating response to neoadjuvant therapy relies on imaging (MRI/CT). However, radiographic evaluations are sometimes unreliable in high-grade sarcomas, due to tumor necrosis, hemorrhage, hyalinization, and fibrosis after neoadjuvant therapy. Conversely, pathology provides a definitive assessment but can only be performed postoperatively. To resolve this problem, minimally invasive biomarkers are required. Circulating tumor DNA (ctDNA) is fragmented, tumor-derived genetic material shed into the bloodstream via apoptosis and necrosis. We investigated whether ctDNA can serve as a biomarker for remaining viable tumor.

Methods: This study is a retrospective, observational study evaluating patients with localized high-grade sarcoma treated at Marshfield Clinic Health System/Sanford Health between January 2020 and December 2024. Eligible patients were required to: have histologically confirmed high-grade sarcoma, complete planned neoadjuvant therapy, and undergo definitive radical resection. Individuals were excluded if they had baseline metastatic disease, or if ctDNA testing at baseline or pre/post-operatively was missing. Pathologic response was graded utilizing the June 2024 CAP Cancer Protocol. Continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables are expressed as counts and percentages.

Results: Out of 39 patients considered, we excluded individuals without sarcoma, without neoadjuvant therapy, with minimal surgical information, or if they were missing ctDNA information. After these exclusions, the analytic dataset included 6 individuals. Of these, 4 were male, 5 had white race, and the median (IQR) age was 75 (66.75,75.75) years. The median (IQR) ctDNA at pre-neoadjuvant therapy, preoperative, and postoperative time points were 2.76 (1.40, 18.81), 0.02 (0, 0.19), and 0.00 (0, 0) Mean Tumor Molecules/mL (MTM/mL) respectively. The median change in ctDNA from pre- to post-neoadjuvant therapy was -2.74 MTM/mL. All 6 patients had a reduction in ctDNA levels from pre- to post-neoadjuvant therapy, but only one patient achieved CR.

Conclusions: This study aims to demonstrate that ctDNA acts as a real time surrogate for neoadjuvant therapy compared to standard imaging. These findings will support clinical use of ctDNA in medical practice for high-grade sarcomas, laying the groundwork for larger prospective clinical trials.