[BIOINFO 2025]

High-Echogenicity Regions Harbor Greater Genomic Complexity: A Radiogenomic Guide for Targeted Breast Biopsy

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Tumor heterogeneity complicates the understanding of cancer and underlies therapeutic resistance, making the accurate sampling of the most representative tumor region both crucial and challenging. While recent multi-omics approaches are emerging to characterize this complexity, a major barrier remains in linking findings from non-invasive imaging to the tumor's molecular characteristics to identify the most significant biopsy locations. Here, we address this challenge by integrating ultrasonography with whole-exome sequencing of 22 paired, spatially distinct samples from 11 breast cancer patients. Our analysis revealed a gene-level pathogenic variant discordancy of 3–12% per patient, as well as notable discordancy within frequently mutated breast cancer genes. Specifically, compared to their low-echogenicity counterparts, high-echogenicity regions were characterized by a higher tumor cell fraction ($P < 0.01$), greater variant allele frequency ($P < 0.001$), increased clonal heterogeneity ($P < 0.05$), and the exclusive presence of key driver mutations. Paradoxically, high underlying genetic complexity was coupled with low radiomic texture heterogeneity, indicating that genomic and radiomic features capture distinct layers of tumor biology. Our findings provide the first evidence of an echogenicity-based radiogenomic link in breast cancer, establishing ultrasound-guided targeting of high-echogenicity regions as a promising strategy to improve the precision of clinical biopsies.