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SCART Modulates the Immune Microenvironment and Enhances Ablative Effects in Murine Hepatocellular Carcinoma Models: Insights from Histopathology and Spatial Transcriptomics

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Abstract

Objectives: Spatially fractionated radiotherapy (SFRT) improves the therapeutic ratio by delivering highly heterogeneous dose distributions to tumors, enabling superior tumor control while sparing normal tissues. As an advanced form of SFRT, SCART (Spatially Compressed Ablative Radiotherapy) has shown promising physical advantages, yet its underlying mechanisms—particularly its immunomodulatory effects on the tumor microenvironment—remain incompletely understood. This study aims to investigate the biological effects of SCART in a murine hepatocellular carcinoma model, with a focus on its role in reprogramming immune spatial architecture and enhancing tumor ablation.

Methods: Subcutaneous H22 hepatocellular carcinoma models were established in BALB/c mice. Treatment commenced when the tumor short axis reached ⩾10 mm and volume ⩾700 mm^3. Mice were allocated into: SCART group (21 Gy × 3 fractions, spatially non-uniform irradiation with peak core dose of 21 Gy and valley dose of 5 Gy at the periphery), SBRT group (uniform 21 Gy × 3), and single-fraction group (21 Gy × 1). Tumors were harvested 72 hours after treatment initiation. Pathological changes (necrosis, immune infiltration) were assessed via H&E staining, and high-definition spatial transcriptomics (0.5 μm resolution) was used to profile gene expression and cellular spatial distribution. Data analysis included differential expression screening, KEGG/GO pathway enrichment, and spatial multimodal integration. Immune cell clusters ($CD45^+$, $PTPRC^+$) were extracted, subjected to unsupervised machine clustering, and annotated using SingleR and AI-assisted cell typing based on marker gene expression and literature references. Multimodal integration was applied to characterize immune cell spatial distribution.

Results: 1. Immune Barrier and Cellular Distribution: Spatial transcriptomics revealed a native immune barrier at the untreated tumor periphery, with significantly lower proportions of $CD8^+$ T cells and macrophages in marginal regions compared to the tumor core.
2. Immune Recruitment Post-Irradiation: SCART irradiation induced substantial immune cell infiltration into peripheral and junctional regions, exceeding the levels observed after SBRT.
3. SCART vs. SBRT: SCART promoted broader activation of immune-related gene expression, higher immune cell density, and reduced dose to normal tissues compared to SBRT.
4. Fractionation Advantage (SCART ×3 vs. ×1): The three-fraction SCART regimen achieved superior 3D conformality compared to single-fraction irradiation.
5. Necrosis and Dosimetric Optimization: The central necrotic volume after three SCART fractions (21 Gy × 3) exceeded the planned 21 Gy isodose volume, expanded compared to single-fraction treatment, and allowed reduced energy output for equivalent ablation, enabling planning target volume reduction.

Conclusion(s): SCART effectively remodels the tumor immune microenvironment by disrupting the peripheral immune barrier and enhancing immune cell recruitment, outperforming conventional SBRT. Fractionated SCART (21 Gy × 3) improves dose conformality, expands central necrosis, and reduces radiation energy requirements. These findings provide immunologic and dosimetric evidence supporting the clinical translation of SCART.