Peritumoral Adipose Tissue as a Prognostic Imaging Biomarker in HNSCC: Integrating Clinical and Molecular Insights

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Introduction: Obesity is a well-known risk factor for many cancers, including head and neck squamous cell carcinoma (HNSCC), yet increased adiposity has been linked to improved responses to immune checkpoint inhibitors (ICIs). Adipose tissue modulates the tumor microenvironment through immune cell infiltration and PD-1 signaling. While prior work has focused on systemic obesity, the role of peritumoral adipose tissue remains unexplored. Understanding how local adiposity impacts PD-1 blockade response may uncover novel mechanisms driving immunotherapy efficacy.

Methods: We performed a retrospective analysis of HNSCC patients (n = 36) treated with neoadjuvant and adjuvant pembrolizumab +/- chemotherapy enrolled in a multi-institutional trial (NCT02641093). Tumors were segmented on pre-treatment contrasted CT scans using 3D Slicer, and a 1 cm peritumoral shell was generated in 24 patients with available imaging. Peritumoral and intratumoral adipose volumes were quantified using patient specific Hounsfield unit thresholds. Adipose metrics included peritumoral adipose fraction (peritumoral adipose volume / peritumoral volume) and the adipose:tumor ratio. Pathologic response was determined histologically. Group differences were tested using Wilcoxon rank-sum and Fisher's exact tests. Survival was censored at 2 years with Kaplan-Meier and log-rank testing. Correlation between adiposity and tumor volume used Spearman's rho. In a subset of patients with paired tissue samples pre- and post-pembrolizumab, RNA-seq data were analyzed for differential pathway enrichment. Gene set enrichment analysis (GSEA) was performed using curated Reactome and KEGG pathways. Pathways were stratified by response status. Analysis was conducted in R (v4.3.1) and two-sided p-values <0.05 were considered statistically significant.

Results: Among 24 patients, median peritumoral adipose fraction was 0.017 (IQR 0.026), median adipose:tumor ratio was 0.096 (IQR 0.194), and the median tumor volume was 8.5 cm^3 (IQR 23.3). Pathologic responders demonstrated significantly higher peritumoral adiposity compared with non-responders (Wilcoxon rank-sum, p = 0.026). When dichotomized by the median, higher peritumoral adiposity was strongly associated with pathologic response (Fisher's exact test, OR = 8.9, 95% CI 1.1-132.4, p = 0.036). Kaplan-Meier analysis with 2-year censoring showed a significantly improved survival in the high-adipose group (2-year OS 100% vs 58% in the low-adipose group; log-rank p = 0.0098). Transcriptomic profiling revealed divergent adipose-driven biological programs between responders and non-responders. Responders exhibited enrichment of lipid metabolism and immunometabolic pathways (SREBP, PPAR alpha, fatty acid metabolism) alongside chemokine/cytokine and TNF signaling, consistent with early immune cell recruitment and activation. In contrast, non-responders showed enrichment of adipocyte differentiation, TGF-beta, TRAF6, and hypoxia pathways, suggesting maladaptive remodeling of the adipose-tumor microenvironment that promotes immune exclusion.

Conclusion: Greater peritumoral adiposity was associated with improved pathologic response and 2-year survival in HNSCC patients treated with pembrolizumab. Transcriptomic analysis suggests that peritumoral adipose tissue may function as a divergent biological regulator, enhancing immune infiltration in some patients while promoting immune evasion in others.

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