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Spatial transcriptional landscape of early-onset tongue cancer

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Motivation and Aim: Tongue squamous cell cancer (TSCC) is characterized by aggressive local invasion and metastasis [1]. The incidence of TSCC among individuals under 45 years of age is growing every year [2]. The etiological factors and pathogenetic mechanisms of TSCC in young adults are poorly understood due to the lack of association with tobacco, alcohol consumption, and HPV [3]. Here, we aimed to investigate the TSCC landscape in patients younger than 45 years of age using spatial transcriptomics.

Methods and Algorithms: The study included 9 TSCC patients with $T_{2\text{-}3}N_{0\text{-}1}M_0$ divided into two groups: under 45 years (n=5) and older than 45 years (n=4). FFPE tumor samples from 4 HPV-negative patients under 45 years and fresh frozen tumor samples from 5 HPV-negative patients (1 patient aged < 45 years and 4 patients aged > 45 years) were profiled using the 10x Genomics Visium Spatial Gene Expression platform. Sequencing was performed on a GenoLab M instrument (GeneMind Biosciences, China) and a NovaSeq 6000 (Illumina, USA). Data integration was performed using the Harmony program package. Seraut package and Enrichr tool were used for clusters identification and gene expression characterization.

Results: A total of 9 clusters were identified with a log2FC > 0.50 and adjusted p-value < 0.0001, which were divided into eight major cell types: two clusters of tumor cells, lymphoid and myeloid immune cells, cancer-associated fibroblasts, muscle, normal epithelium, and salivary gland cells. In early-onset TSCC, tumor clusters were enriched by increased expression of mitogen activated kinase (MAPK) pathway genes: *EGR1*, *IL1B*, *MAP2K1*, *MAP2K3*, *FOS*, *FOSB*, *JUN*, *JUNB*, *FOSL1*, and *FOSL2* (log2FC > 0.57 and adjusted p-value < 0.0001) compared to late-onset cancer. At the same time, there was a decreased expression of oxidative phosphorylation genes (*ATF5PF*, *SDHD*, *GBP5*, *NDUFA3*, *UQCR11*, *COX7B*, *S100A7*, log2FC > 0.48 and adjusted p-value < 0.0001) and increased expression of glycolysis marker *PFKFB3* (log2FC > 0.74 and adjusted p-value < 0.0001) in young adults TSCC. The border between tumor and normal tissue in the TSCC of young adults was enriched with vascular mimicry with increased expression of JAK-STAT signaling pathway genes (*TGA5*, *ITGB1*, *MAP2K3*, *STAT3*, *MYC*, *EPHA2*, *FN1*, *MMP14*, *COL1A1*; log2FC > 0.61 and adjusted p-value < 0.0001). In addition, regions of vascular mimicry were enriched with tumor-associated macrophage markers: *CD68*, *SERPINB2* and *OSM*.

Conclusion: TSCC in young adults has distinct spatial transcriptomic features compared to late-onset tongue cancer including enrichment of MAPK and JAK-STAT signaling pathways and TAMs and vascular mimicry at the invasive front as well as downregulation of oxidative phosphorylation and upregulation of glycolysis.
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