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Determining the relationships between quantitative HPV DNA liquid biopsy results and circulating immune cell populations in HPV-positive head and neck squamous cell carcinoma

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Background/Objectives: Assays that detect circulating tumor HPV DNA (ctHPVDNA) have shown promise in monitoring treatment response and disease recurrence/progression. Understanding the relationship between ctHPVDNA levels and immune cell populations could provide additional insight into the immune landscape of HPV+ HNSCC and its implications for prognosis and therapy. The objective was to evaluate the relationship between ctHPVDNA levels (quantitative and categorical readouts) and circulating immune cell populations in patients with HPV+ HNSCC to identify potential prognostic biomarkers that could better predict treatment response and clinical outcomes.

Methods: We conducted a retrospective study on a preliminary cohort of patients (n=35) with confirmed HPV+ HNSCC (p16+) and detectable pre-treatment ctHPVDNA (NavDx, Naveris, Waltham, MA). We included patients who received surgery (n=7), chemotherapy (n=26), or radiotherapy (n=28) as their primary treatment. We quantified ctHPV-DNA in the pre-treatment, on-treatment, post-treatment, and surveillance settings. A routine complete blood count (CBC) with differential analysis was collected around the corresponding ctHPV-DNA test and was used to determine neutrophil, lymphocyte, monocyte, and immature granulocyte relative percentages and absolute counts. Three primary analyses were performed on this dataset: (1) correlation between pre-treatment log-transformed ctHPVDNA levels and immune cell populations (n=35), (2) percent changes among immune cell profiles in response to treatment (pre-treatment ctHPV-DNA positive vs first undetectable, n=20), and (3) response to recurrence/progression (any ctHPVDNA level increase vs previous result, n=8 events across six patients). Significance was determined via correlation analyses or by performing wilcoxon matched-pairs signed rank test.

Results: Our analyses revealed a significant negative correlation between pre-treatment ctHPVDNA levels (average=2590, SD=5185) and the relative percentage of immature granulocytes (R=-0.3773, p=0.0278). We also observed correlations between pre-treatment ctHPVDNA levels and absolute counts of immature granulocytes (R=-0.2321, p=0.1865) and monocytes (R=0.1414, p=0.4178) for which significance might become evident in a larger cohort of patients. In response to primary treatment (n=20, pre-treatment ctHPVDNA positive vs. first undetectable, average=92 days, SD=53 days), there was a 50.8% reduction in absolute lymphocyte counts (p<0.0001, n=20). This effect appears consistent regardless of primary treatment type, including surgery. Secondly, in the post-treatment and surveillance setting, there was a 43.3% increase in absolute lymphocyte counts accompanying increasing ctHPVDNA levels (p=0.0469, n=8). Of these, 3/8 were negative to positive (78.3% increase), while the other 5/8 were elevated positive results (22.3% increase). These findings suggest that relative changes in absolute lymphocyte counts over time could serve as a patient-specific biomarker to better define HPV+ HNSCC response to treatment and disease recurrence or progression.

Conclusions: This study provides evidence that ctHPVDNA levels, when combined with immune cell population data, may offer a more comprehensive view of cancer dynamics in HPV+ HNSCC. The relationship between ctHPVDNA levels and immune cell subsets, mainly lymphocytes, could serve as an additional biomarker for monitoring treatment response and disease recurrence or progression.