Circulating Tumor HPV DNA for Surveillance of HPV+ Sinonasal Squamous Cell Carcinoma

Elise Krippaehne, BS[1], Vivek Pandrangi, MD[1], Mathew Geltzeiler, MD[1]
[1] Oregon Health & Science University, Department of Otolaryngology-Head & Neck Surgery, Division of Rhinology and Skull Base Surgery

Introduction

- Human papillomavirus positive (HPV+) sinonasal squamous cell carcinoma (SNSCC) has a high recurrence rate, often within the first two years post-treatment[1], necessitating intensive surveillance.
- However, post-treatment inflammation can complicate imaging interpretation, and there is no standardized surveillance protocol for SNSCC.
- Circulating tumor HPV DNA (ct-HPVDNA) is a promising non-invasive biomarker. Studies in HPV+ oropharyngeal squamous cell carcinoma (OPSCC) have demonstrated high sensitivity and specificity of ct-HPVDNA[2], with potential applications in SNSCC.
- This case report explores ct-HPVDNA's utility for post-treatment monitoring and surveillance of SNSCC.

Case Report

- 58-year-old male with history of right-sided sinonasal inverted papilloma (IP) with high-grade dysplasia (HGD) s/p endoscopic resection at an outside facility 7 months prior who presented with persistent nasal obstruction and intermittent epistaxis.
- CT revealed a 4.4 x 2.6 x 1.2 cm R nasal cavity mass.
- Second endoscopic resection confirmed a broad-based IP with focal invasive SCC. Surgical margins were negative, and no adjuvant therapy was required.
- Surveillance with MRI scans and clinical evaluations every 3 months was initiated. Serial MRIs showed stable postsurgical changes.
- However, 2.5 years postoperatively, endoscopy revealed erythematous mucosa at the middle turbinate stump. Biopsies confirmed recurrent high-grade dysplasia with focal SCC.
- PET/CT showed uptake in the L posterior nasopharynx (**Figure 1**) and mild to moderate uptake in sub-centimeter bilateral level II cervical lymph nodes. FNA of these lymph nodes was negative.
- ct-HPVDNA testing was positive (score: 5, p16+) prompting endoscopic resection. **Table 1** provides the ct-HPVDNA score interpretation.
- Primary lesion extended from the nasal septum to the ethmoid roof and posteriorly into the sphenoid sinus with additional lesions at the nasopharynx.
- Immunohistochemistry was positive for squamous markers (p40, p63 and CK5/6), diffusely positive for p16, and negative for Epstein-Barr virus. Margins were negative, and ct-HPVDNA 2 weeks post-op returned negative.
- Adjuvant proton therapy was deferred in favor of close surveillance.
- Patient remained asymptomatic, however, 2 years later, ct-HPVDNA returned positive (score: 8). **Figure 4** demonstrates ct-HPVDNA surveillance.
- PET/CT (**Figure 2**) identified a 15 x 11 mm nasal cavity mass and a 13 x 8 mm R lateral retropharyngeal lymph node. T1 MRI (**Figure 3**) confirmed these findings. Biopsies confirmed p16+ HGD/carcinoma in situ.
- Proton therapy was initiated given concern for metastatic disease.

Figure 1. PET/CT 2.5 years post-op demonstrating intense focal FDG activity in the L posterior nasopharynx.

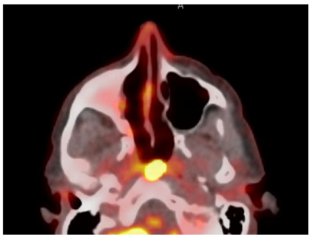


Figure 2. PET/CT during most recent surveillance visit demonstrating – **(A)** Focal uptake in the R posterior nasal cavity; **(B)** and in the R retropharyngeal space.

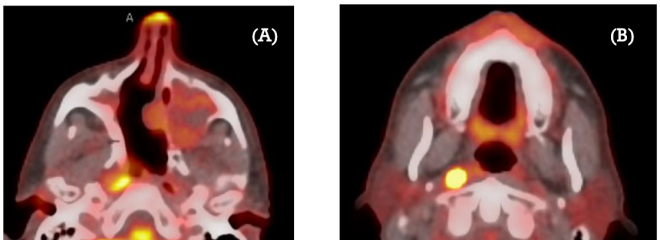


Figure 3. T1 MRI during most recent surveillance visit demonstrating – **(A)** Enhancing soft tissue nodule along the R posterior nasal passage corresponding to uptake seen in PET/CT; **(B)** and R lateral retropharyngeal lymph node.

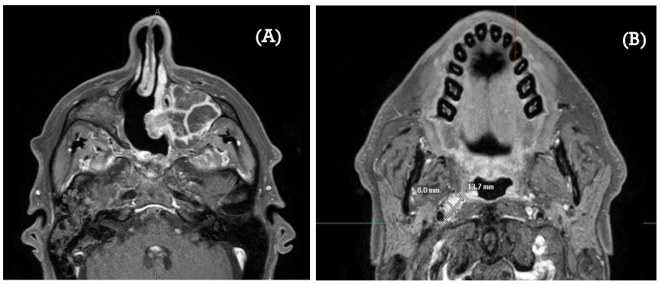
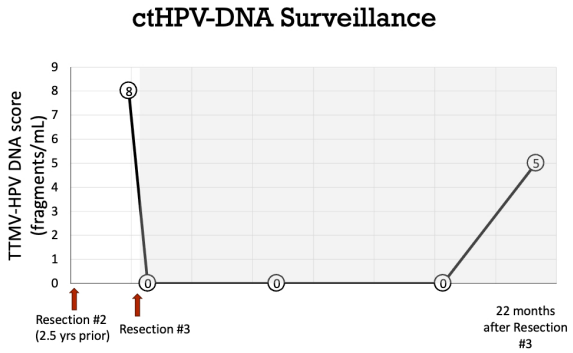


Table 1. Interpretation of ctHPV-DNA scores.

TTMV-HPV 16 DNA Score	TTMV-HPV 18, 31, 33, 35 DNA Score	Risk Score Interpretation
< 2	<5	Negative
2-3	5-12	Indeterminate
>3	>12	Positive

Figure 4. Liquid biopsy surveillance



Discussion

- In this case, ct-HPVDNA testing identified residual disease prior to overt clinical or radiological findings, demonstrating its utility in detecting recurrence at a subclinical stage.
- While ct-HPVDNA is well-established for monitoring HPV-related OPSCC, its application in SNSCC remains underexplored. Traditional monitoring relies on a combination of clinical examinations, nasal endoscopy, and imaging; however, these methods may not always detect recurrence at an early stage.
- ct-HPVDNA testing offers several advantages. As a simple blood-based assay, it reduces patient discomfort, and the risks associated with invasive biopsies. Additionally, it has been shown to shorten the median diagnostic interval to 26 days or less and reduce overall surveillance costs by 36-38% compared to traditional clinical workups[3], which often involve multiple imaging studies and physical examinations.
- However, ct-HPVDNA is not intended to replace imaging but rather to serve as a complementary tool within an established surveillance framework.

Conclusions

- This case underscores the potential for integrating ct-HPVDNA into surveillance protocols for HPV-positive SNSCC, as it may contribute to more accurate assessments of treatment response and recurrence, ultimately enhancing patient management strategies.
- Further research with larger cohorts is needed to standardize ct-HPVDNA testing in SNSCC, including defining thresholds for clinical action, optimizing testing frequency, and assessing cost-effectiveness in routine practice.

CONTACT
Mathew Geltzeiler, MD
Email: geltzeil@ohsu.edu

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