Accepted Manuscript online: 2025-04-08 Article published online: 2025-04-25

Circulating Tumor DNA Testing for Detection and Surveillance of Sinonasal HPV-Associated Cancers

Avraham E. Adelman[1] Kartik Motwani[1] Nikita Chapurin[1]

[1] Department of Otolaryngology—Head and Neck Surgery, University of Florida, Gainesville, Florida, United States

J Neurol Surg Rep 2025;86:e89–e91.

Address for correspondence Nikita Chapurin, MD, MHS, Department of Otolaryngology, H&N Surgery, University of Florida, 1345 Center Dr, M228 MSB, PO Box 100264, Gainesville, FL 32610, United States (e-mail: nikita.chapurin@ent.ufl.edu).

Abstract

Background The incidence of human papilloma virus (HPV)-mediated head and neck (H/N) cancers has risen dramatically. While most HPV-associated H/N cancers are oropharyngeal squamous cell carcinoma (OPSCC), sinonasal squamous cell carcinoma (SNSCC) is the second most common. Recent studies highlight an increasing incidence of HPV-positive SNSCC. Circulating tumor HPV DNA (ctDNA) is a noninvasive tool that has become increasingly utilized to detect high-risk HPV genotypes in the setting of OPSCC, with recent studies reporting high sensitivity and specificity in both pretreatment detection and posttreatment surveillance in OPSCC. Only one study exists reporting its use for SNSCC and nasopharyngeal carcinoma, which was successful in pretreatment detection and identification of recurrence posttreatment.

Case Reports We report two cases demonstrating the utility of ctDNA in HPV-mediated sinonasal malignancies. Case 1: 60-year-old male who presented with a large nasal cavity cancer. Pretreatment ctDNA testing yielded a positive tumor tissue modified viral (TTMV)-HPV DNA Score of 67, reflective of the normalized tumor tissue modified viral-HPV DNA fragments/mL of plasma, and pathology confirmed HPV+ SNSCC. Posttreatment surveillance with HPV ctDNA and endoscopy has shown no evidence of disease. Case 2 involves a 64-year-old male with HPV+ neuroendocrine carcinoma who developed recurrence. ctDNA testing, previously negative following initial treatment, scored 35 at recurrence, prompting salvage surgery and adjuvant chemoradiation.

Conclusion These cases, along with prior studies, underscore the potential of ctDNA as a diagnostic and surveillance tool for sinonasal malignancies. Further multi-institutional prospective trials with larger cohorts are needed to validate its role in detection and surveillance.

Keywords

- circulating tumor DNA
- HPV
- sinonasal carcinoma
- sinonasal squamous cell carcinoma
- liquid biopsy

Introduction

Over recent decades, the incidence of human papilloma virus (HPV+)-associated head and neck (H/N) cancer has risen dramatically and now surpasses that of cervical cancer.[1] Most HPV+ H/N cancers are oropharyngeal squamous cell carcinoma (OPSCC), but the sinonasal tract is the second most common site.[1] Sinonasal or nasopharyngeal tumors with a

received
February 28, 2025
accepted
March 19, 2025
accepted manuscript online
April 8, 2025

DOI https://doi.org/10.1055/a-2576-7496.
ISSN 2193-6358.

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

Table 1 Circulating HPV tumor DNA performance in head and neck cancer

Indication	*n*	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	Reference
Diagnosis	97	95.9% (NR)	100% (NR)	NR	NR	[8]
Diagnosis	163	91.5% (85.8–95.4%)	100% (71.5–100%)	NR	NR	[9]
Surveillance	290 (591 tests)	88.4% (74.9–96.1%)	100% (99.3–100%)	100%	99%	[9]
Diagnosis	72	97.2% (90.3–99.6%)	100% (47.8–100%)	100%	71.4%	[10]
Surveillance	54 (219 tests)	100% (59–100%)	87% (74.3–95.2%)	NR	NR	[10]
Diagnosis	141	91.7% (NR)	100% (NR)	100%	63.6%	[11]
Diagnosis	140	98.4% (NR)	98.6% (NR)	98.4%	98.6%	[12]
Surveillance	115 (10,006 tests)	100% (NR)	99% (NR)	94%	100%	[13]

Abbreviations: CI, confidence interval; HPV, human papilloma virus; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

capacity for HPV-oncogenesis include sinonasal squamous cell carcinoma (SNSCC), nasopharyngeal carcinoma (NPC), neuroendocrine carcinoma, and HPV-related multiphenotypic carcinoma.[2] In particular, recent studies show an increasing incidence of HPV+ SNSCC, despite a decline in HPV testing.[3–5]

"Liquid biopsy" is the noninvasive testing of body fluids (e.g. plasma) for tumor components, with biomarkers that include circulating tumor DNA (ctDNA), tumor cells, and microRNAs.[6] NavDx (Naveris) is a commercially available assay that detects high-risk HPV-ctDNA genotypes (HPV-16, HPV-18, HPV-31, HPV-33, and HPV-35).[7] The NavDx test result provides a "score" that represents the normalized tumor tissue-modified viral-HPV DNA fragments/mL of plasma.[7] In HPV+ OPSCC, ctDNA has been increasingly utilized for diagnosis, treatment response monitoring, and posttreatment surveillance.

Recent studies demonstrate high sensitivity and specificity of ctDNA testing for HPV+ OPSCC, with pretreatment detection sensitivity and specificity ranging from 91.5 to 98.4% and 98.6 to 100%, respectively (►**Table 1**).[8–12] For posttreatment surveillance, sensitivity and specificity range from 88.4 to 100% and 87.2 to 100%, respectively (►**Table 1**).[9,10,13]

However, there is limited research investigating ctDNA for HPV+ SNSCC or NPC. The only known report included five HPV+ NPC and four HPV+ SNSCC patients with detectable baseline ctDNA.[14] In six patients followed posttreatment, two recurrences were detected by ctDNA before clinical detection.[14]

Case Presentation

Case 1

A 56-year-old male presented with nasal obstruction and epistaxis. Endoscopy and imaging revealed a large sinonasal mass arising from the septum, filling the entire nasal cavity, with erosion of the right cribriform skull base (►**Fig. 1A, B**). Biopsy confirmed p16+ SNSCC and baseline ctDNA score was 67 (reference range: 0–5), subtype HPV-33. Negative margin expanded endonasal resection was performed. The tumor was p16+ on immunohistochemistry and high-risk HPV mRNA+ via in situ hybridization. Postoperative ctDNA was negative, and after adjuvant proton radiotherapy (6,400 cGy), surveillance with endoscopy and ctDNA continued to indicate no evidence of disease at 4 months (►**Fig. 1C**).

Case 2

A 64-year-old male with a history of left neck level II HPV+ neuroendocrine carcinoma of unknown primary origin (presumed OP), presented 9 months postradiotherapy with a new sinonasal mass arising from the olfactory cleft and involving the anterior skull base (►**Fig. 2A, B**), consistent

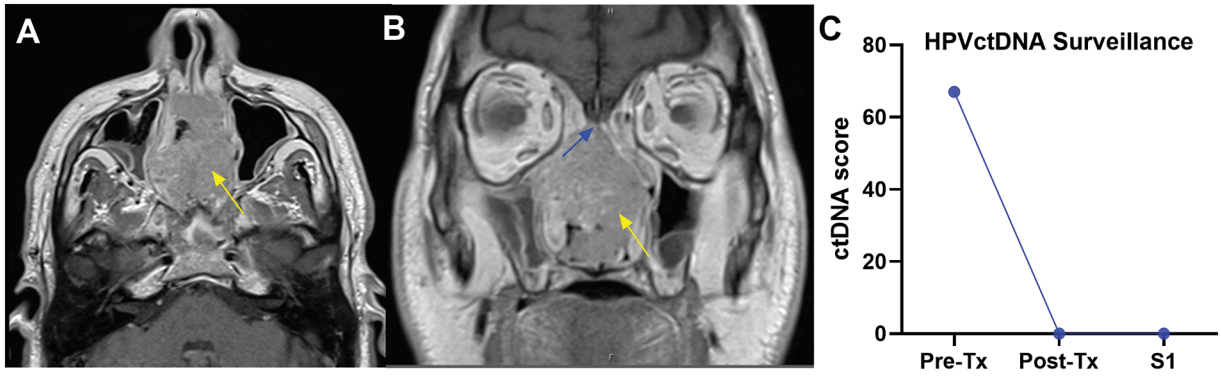

Fig. 1 Axial (**A**) and coronal (**B**) views of maxillofacial MRI T1 with contrast demonstrating very large SNSCC filling the entire nasal cavity (yellow arrows), extending toward bilateral orbits, and causing bony erosion of right anterior skull base (blue arrow). Serial NavDx tests (**C**) show elevated ctDNA level pretreatment with no evidence of recurrence during the surveillance period following resection. SNSCC, sinonasal squamous cell carcinoma; ctDNA, circulating tumor DNA; MRI, magnetic resonance imaging; Tx, treatment; S1, surveillance #1.

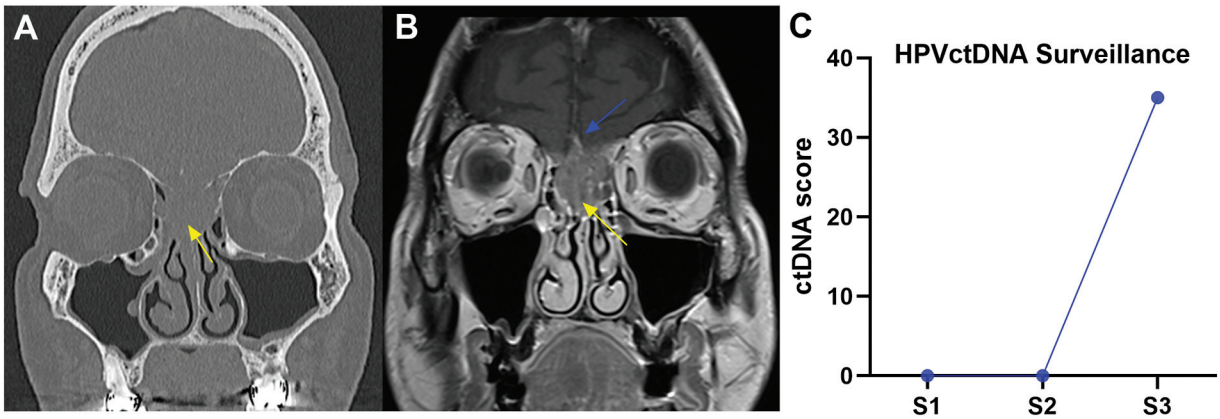

Fig. 2 Coronal views of maxillofacial CT without contrast (**A**) and MRI T1 with contrast (**B**) demonstrate recurrent sinonasal neuroendocrine carcinoma (yellow arrows) arising from the olfactory cleft and involving the anterior skull base, with transdural involvement of cribriform/olfactory tract (blue arrow). NavDx tests (**C**) accurately captured the recurrence of the tumor, with elevated ctDNA in the third surveillance period. CT, computed topography; MRI, magnetic resonance imaging; ctDNA, circulating tumor DNA; S1/S2/S3, surveillance #'s 1, 2, and 3.

with a previously undetected primary tumor. Surveillance ctDNA had been negative until then (score: 0) but at the time of recurrence presentation, scored 35 (reference range: 0–5), subtype HPV-18 (►**Fig. 2C**). He underwent salvage surgery with adjuvant chemoradiation.

Conclusion

There is scarce published data on ctDNA testing in sinonasal tumors. We present two cases demonstrating ctDNA's ability to surveil HPV-mediated sinonasal malignancies posttreatment and successfully correlate with tumor recurrence. These cases demonstrate the potential of HPV-ctDNA for the detection, monitoring of treatment response, and surveillance of HPV+ sinonasal cancers. Current challenges to implementation include limited available data and institutional access to testing kits. Multi-institutional prospective trials are needed to definitively assess the sensitivity/specificity of ctDNA testing as well as cost-benefit analysis comparing this surveillance strategy to the current standard of care.

Conflict of Interest

None declared.

References

1 Lechner M, Liu J, Masterson L, Fenton TR. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol 2022;19(05):306–327
2 Chan JK. Virus-associated neoplasms of the nasopharynx and sinonasal tract: diagnostic problems. Mod Pathol 2017;30(s1): S68–S83
3 Amanian A, Ishii M, Fakhry C, London NR Jr. Epidemiologic trends in human papillomavirus-associated sinonasal squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg 2024;150(07):609–618
4 Barlow J, Gilja S, Ferrandino RM, et al. Evaluating human papillomavirus testing, prevalence, and association with prognosis in head and neck squamous cell carcinoma by subsite: a national cancer database study. Am J Otolaryngol 2024;45(03): 104243
5 Costantino A, Haughey B, Zhu J, et al. Sinonasal squamous cell carcinoma in the United States: temporal and geographic patterns associated with HPV testing and positivity. Oral Oncol 2024; 154:106855
6 Cabezas-Camarero S, Pérez-Segura P. Liquid biopsy in head and neck cancer: current evidence and future perspective on squamous cell, salivary gland, paranasal sinus and nasopharyngeal cancers. Cancers (Basel) 2022;14(12):20220609
7 Gunning A, Kumar S, Williams CK, et al. Analytical validation of NavDx, a cfDNA-based fragmentomic profiling assay for HPV-driven cancers. Diagnostics (Basel) 2023;13(04):20230214
8 Damerla RR, Lee NY, You D, et al. Detection of early human papillomavirus-associated cancers by liquid biopsy. JCO Precis Oncol 2019;3:20190403
9 Ferrandino RM, Chen S, Kappauf C, et al. Performance of liquid biopsy for diagnosis and surveillance of human papillomavirus-associated oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 2023;149(11):971–977
10 Jakobsen KK, Bendtsen SK, Pallisgaard N, et al. Liquid biopsies with circulating plasma HPV-DNA measurements-a clinically applicable surveillance tool for patients with HPV-positive oropharyngeal cancer. Clin Cancer Res 2023;29(19):3914–3923
11 Mijares K, Ferrandino R, Chai R, et al. Circulating tumor HPV DNA in patients with head and neck carcinoma: correlation with HPV genotyping. Am J Surg Pathol 2024;48(01):80–87
12 Siravegna G, O'Boyle CJ, Varmeh S, et al. Cell-free HPV DNA provides an accurate and rapid diagnosis of HPV-associated head and neck cancer. Clin Cancer Res 2022;28(04):719–727
13 Chera BS, Kumar S, Shen C, et al. Plasma circulating tumor HPV DNA for the surveillance of cancer recurrence in HPV-associated oropharyngeal cancer. J Clin Oncol 2020;38(10):1050–1058
14 Naegele S, Efthymiou V, Das D, et al. Detection and monitoring of circulating tumor HPV DNA in HPV-associated sinonasal and nasopharyngeal cancers. JAMA Otolaryngol Head Neck Surg 2023;149(02):179–181