Association of Circulating Tumor DNA Levels with Adverse Pathologic Features in HPV+ Oropharynx Cancer

Jacob Beiriger, BS; Birk Olson, MD; Nilam Patel, MD; Marcus M Monroe, MD; Richard B Cannon, MD; Hilary C. McCrary, MD

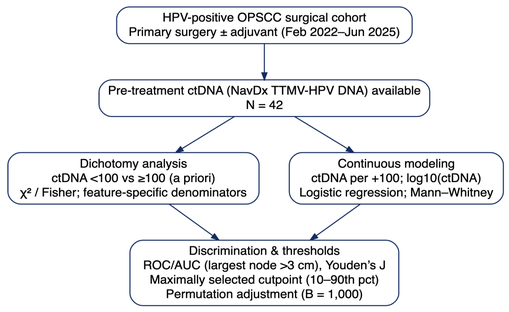
Department of Otolaryngology – Head and Neck Surgery, Huntsman Cancer Institute
University of Utah

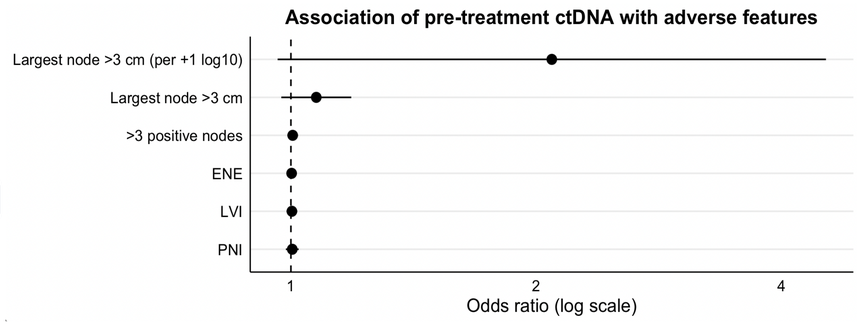
INTRODUCTION

- HPV+ OPSCC adjuvant decisions depend on adverse pathology (PNI, LVI, ENE, nodal number/size)
- It is unclear if **pre-treatment TTMV-HPV DNA (NavDx)** correlates with these features
- **Objectives**
  - Compare **<100 vs ≥100 fragments/mL** groups
  - Analyze ctDNA as a **continuous** and **log10** measure
  - Identify **useful operating thresholds** for risk stratification

METHODS

- **Design/Setting:** Retrospective institutional surgical cohort
- **Population:** HPV+ OPSCC with **pre-treatment NavDx** and primary surgery ± adjuvant, **N=42**, (2022 to 2025)
- **Outcomes:** PNI, LVI, ENE, **>3 positive nodes**, **largest node >3 cm**; secondary = **any adverse feature**
- **Biomarker cutoff for grouping:** Low **<100 vs** High **≥100**
- **Statistics:** χ^2 or Fisher; Mann–Whitney; **logistic regression**; **ROC/AUC** with **Youden's J**; **maximally selected cutpoint** scan (10th–90th percentile, ≥8 per group)
- **Software:** R 4.5.1 GUI 1.82 High Sierra build (8536)





RESULTS

- 42 HPV+ OPSCC patients with pre-treatment TTMV-HPV DNA. Age 63.5 y (IQR 57.5–72.0); 81% male.
- No significant differences in PNI, LVI, ENE, >3 nodes, or largest node >3 cm (feature-specific reported in Table 1).
- Pre-treatment ctDNA (per **+1 log10**) associated with **largest node >3 cm**: OR **2.09** (95% CI 0.96–4.53), **p=0.062**; other endpoints showed no signal.
- ROC for predicting **largest node >3 cm**: **AUC 0.654** (n=36).
  - **100** fragments/mL: Sens 0.60, Spec 0.67, PPV 0.56, NPV 0.70.
  - **Empiric cutpoint ~1,237**: Sens 0.47, Spec 0.95, PPV 0.88, NPV 0.71.
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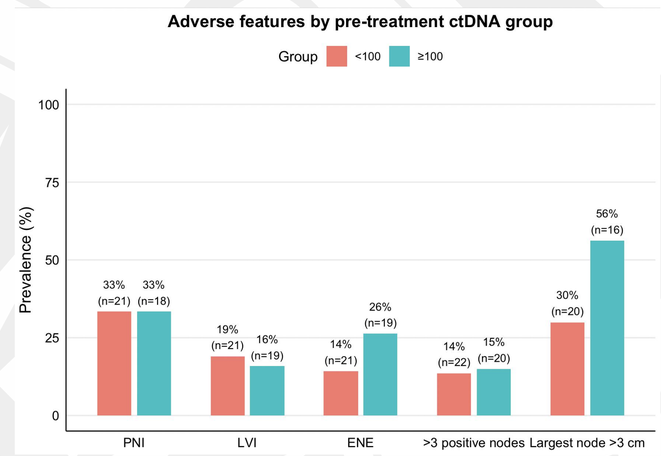
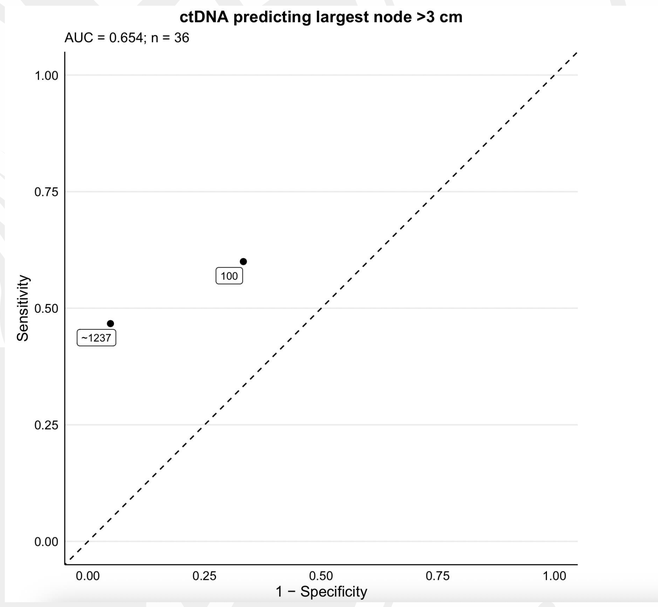
Variable	Value
Age, years	median 63.5 (IQR 57.5–72.0); n=42
Sex — Male	34 (81.0%)
Sex — Female	8 (19.0%)
Race — White	41 (97.6%)
Race — Unknown/Not disclosed	1 (2.4%)
Ethnicity — Not Hispanic/Latino	40 (95.2%)
Ethnicity — Not disclosed/Unknown	2 (4.8%)
History of tobacco smoking — Yes	17 (41.5%)
History of alcohol use — Yes	25 (62.5%)
Primary site — Tonsil	23 (54.8%)
Primary site — Base of tongue	14 (33.3%)
Primary site — 5 (unknown primary)	2 (4.8%)
Primary site — Oropharynx	1 (2.4%)
Primary site — 5 (pyriform sinus)	1 (2.4%)
Primary site — 1, 2	1 (2.4%)
Pathologic T — T1	17 (40.5%)
Pathologic T — T2	22 (52.4%)
Pathologic T — T3	1 (2.4%)
Pathologic N — N0	7 (16.7%)
Pathologic N — N1	31 (73.8%)
Pathologic N — N2	3 (7.1%)
Pathologic stage — I	37 (88.1%)
Pathologic stage — II	4 (9.5%)





Discussion

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CONCLUSIONS

- A simple <100 vs ≥100 comparison is not informative in this surgical cohort. ctDNA as a continuous marker yields a rule-in operating point (~1,237) identifying patients enriched for large nodal size at pathology.[1,2]
- ctDNA's strongest utility here is specificity: high pre-treatment values select patients more likely to harbor bulky nodal disease; low values do not reliably exclude adverse features. [2,3]
- TTMV-HPV DNA is established for surveillance/recurrence detection, whereas pre-treatment risk-stratification remains less defined; our data support exploring ctDNA-guided surgical/adjuvant decision aids.[1,2,4]

References:

1. Berger BM, Hanna GJ, Posner MR, **et al.** Detection of occult recurrence using circulating tumor tissue modified viral HPV DNA among patients treated for HPV-driven oropharyngeal carcinoma. *Clin Cancer Res.* 2022;28(19):4292-4301. doi:10.1158/1078-0432.CCR-22-0562.
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3. Ferrandino RM, Barlow J, Gold B, **et al.** Diagnostic accuracy of circulating tumor HPV DNA testing in patients with a lateral neck mass. *JAMA Otolaryngol Head Neck Surg.* 2024;150(12):1089-1096. doi:10.1001/jamaoto.2024.2702.
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5. Agarwal A, Bhatt A, Patel S, Bathla G, Murray J, Rhyner P. Preliminary results from retrospective correlation of circulating tumor DNA with imaging for HPV-positive oropharyngeal squamous cell carcinoma. *AJNR Am J Neuroradiol.* 2024;45(8):1135-1140. doi:10.3174/ajnr.A8242.