Viral Load Surveillance and Disease Recurrence in HPV-Positive Oropharyngeal Cancer: A Systematic Review and Meta-Analysis

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Background

- HPV-positive OPSCC has increased over the past two decades and now represents >70% of all OPSCC cases in the U.S.
- Despite better treatment response than HPV-negative disease, 10–20% of HPV-positive OPSCC cases recur
- Current surveillance relies on H&P, oropharyngeal visualization via nasopharyngeal laryngoscopy, and PET imaging, per NCCN guidelines

70% — Newly diagnosed OPSCC is HPV +

10-20% — Recurrence in HPV+ OPSCC

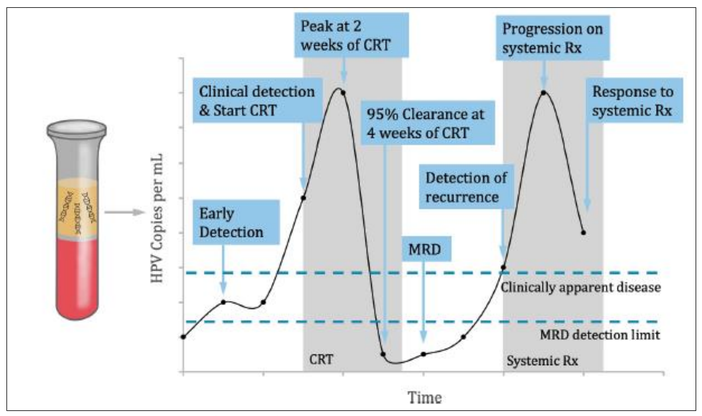
About ctDNA

Circulating Tumor DNA (ctDNA) measures the fragmented DNA present in the acellular component of blood and fluids

In the context of HPV-positive oropharyngeal cancer, ctDNA assays target E6 and E7 oncogene regions and high-risk genotypes such as HPV 16 and 18

ctDNA in Cancer Surveillance

- CtDNA in plasma is an emerging biomarker with studies supporting baseline positivity in 90% of patients at diagnosis, predictable kinetics with treatment, and early detection of recurrence.



Source: Haring et al. The future of circulating tumor DNA as a biomarker in HPV related oropharyngeal squamous cell carcinoma, Oral Oncology, Volume 126, 2022, 105776, ISSN 1368-8375)

Research Question

"In patients with HPV-positive OPSCC, does the presence of HPV in serum plasma after treatment predict the risk of disease recurrence?"

Methods

- PRISMA-compliant systematic review and meta-analysis
- Quality assessments using Oxford Centre for Evidence-Based Medicine (CEBM) and Newcastle-Ottawa Scale (NOS)
- Pooled sensitivity, specificity, and AUC calculated using a bivariate random-effects (Reitsma) model in R, applying continuity corrections for zero cells and reporting 95% CIs. Heterogeneity calculated via I^2, Zhou & Dendukuri method

Search Strategy

PICOT Framework

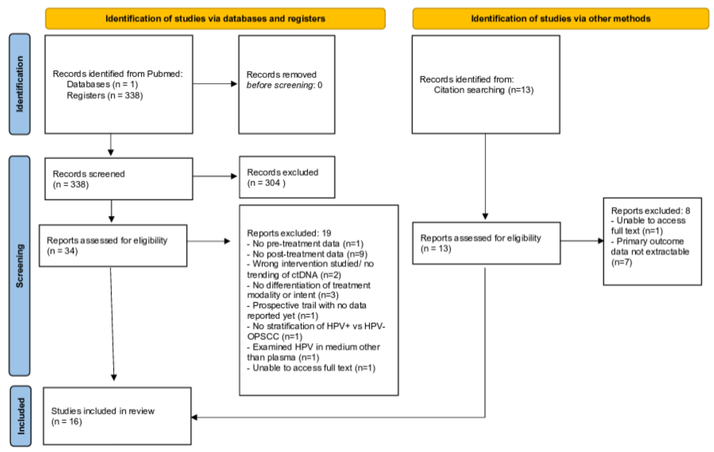
- **Population:** HPV-positive OPSCC
- **Intervention:** treatment with curative intent
- **Comparator:** ctDNA
- **Outcome:** Recurrence
- **Time:** < 20 Years

Inclusion Criteria

- Baseline ctDNA positivity in plasma prior to completion of treatment
- At least one post-treatment ctDNA assessment
- Outcome reporting of recurrence confirmed by imaging or biopsy

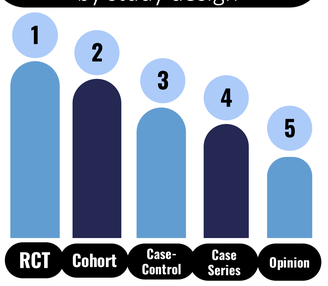
Exclusion Criteria

- HPV-driven squamous cell carcinoma outside the oropharynx
- Unresectable disease or palliative-only treatment



Quality and Bias

CEBM: level ranked by study design



NOS: assess quality of cohort studies

- 0-4 **Selection**
  - Representativeness of the exposed cohort
  - Ascertainment of exposure
- 0-2 **Comparability**
  - Controls and documentation of confounding variables
- 0-3 **Outcome**
  - Assessment of outcome
  - Adequacy of follow up

Results: Quality and Bias

- Overall evidence of adequate quality with low risk of bias, but one weaker study was included
- Cao 2012 → CEBM Level 4 → unable to assess via NOS

15/16 — Cohort Studies: CEBM Level 2

15/16 — NOS: 5-8 Stars (Moderate Quality)

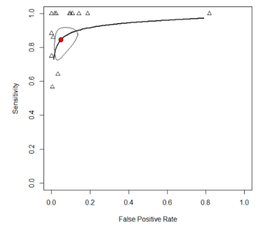
1/16 — Case Series

Results: Meta-Analysis

Studies included: 16

Total patients: 2,524

Total tests: 3,090

Pooled Sensitivity and Specificity (CI 95%)	sensitivity **84.6%** (95% CI: 75.4–90.7%) specificity **95.2%** (95% CI: 88.9–98.0%)
NPV and PPV (CI 95%)	NPV **98.2%** (95% CI: 97.2–98.9%) PPV **65.6%** (95% CI: 46.4–82.1%)
Prevalence	**9.84%** (95% CI 8.39 - 11.51%)
Odds Ratio (CI 95%)	171 (95% CI 73-400)
Heterogeneity (I^2)	I^2 = 7.7%
Area Under Receiver Operator Curve (AUC)	AUC = 0.933
Receiver Operator Curve (ROC)	

Conclusions

Strengths

- **Low heterogeneity (7.7%)** enabled pooling of **3,090 tests from 2,524 patients**, the **largest meta-analysis to date**.
- **NPV 98.2% (95% CI: 97.2–98.9%)** and **ROC/AUC near 1.00** show ctDNA is an excellent "rule-out" test.

Limitations

- **PPV 65.6% (95% CI: 46.4–82.1%)** should be interpreted cautiously with confirmatory PET/CT before management changes
- Variability of **ctDNA detection assays** hinders standardization and clear detection thresholds

- NCCN guidelines outline follow-up schedules, imaging, labs, and dental care for OPSCC, but **do not address ctDNA**
- ctDNA has excellent NPV, provides added reassurance, and may **complement standard NCCN surveillance**

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References

Available from the corresponding author upon request.