2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
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Does ctDNA Needs to be Included in the Management of HPV-Related OPSCC? Yes!

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MAGICALQUOTE

IT'S A DANGEROUS **BUSINESS**, GOING OUT YOUR **DOOR**. YOU **STEP** ONTO THE **ROAD**, AND IF YOU DON'T KEEP YOUR **FEET**, THERE'S NO KNOWING WHERE YOU MIGHT BE **SWEPT** OFF TO.

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BILBO BAGGINS

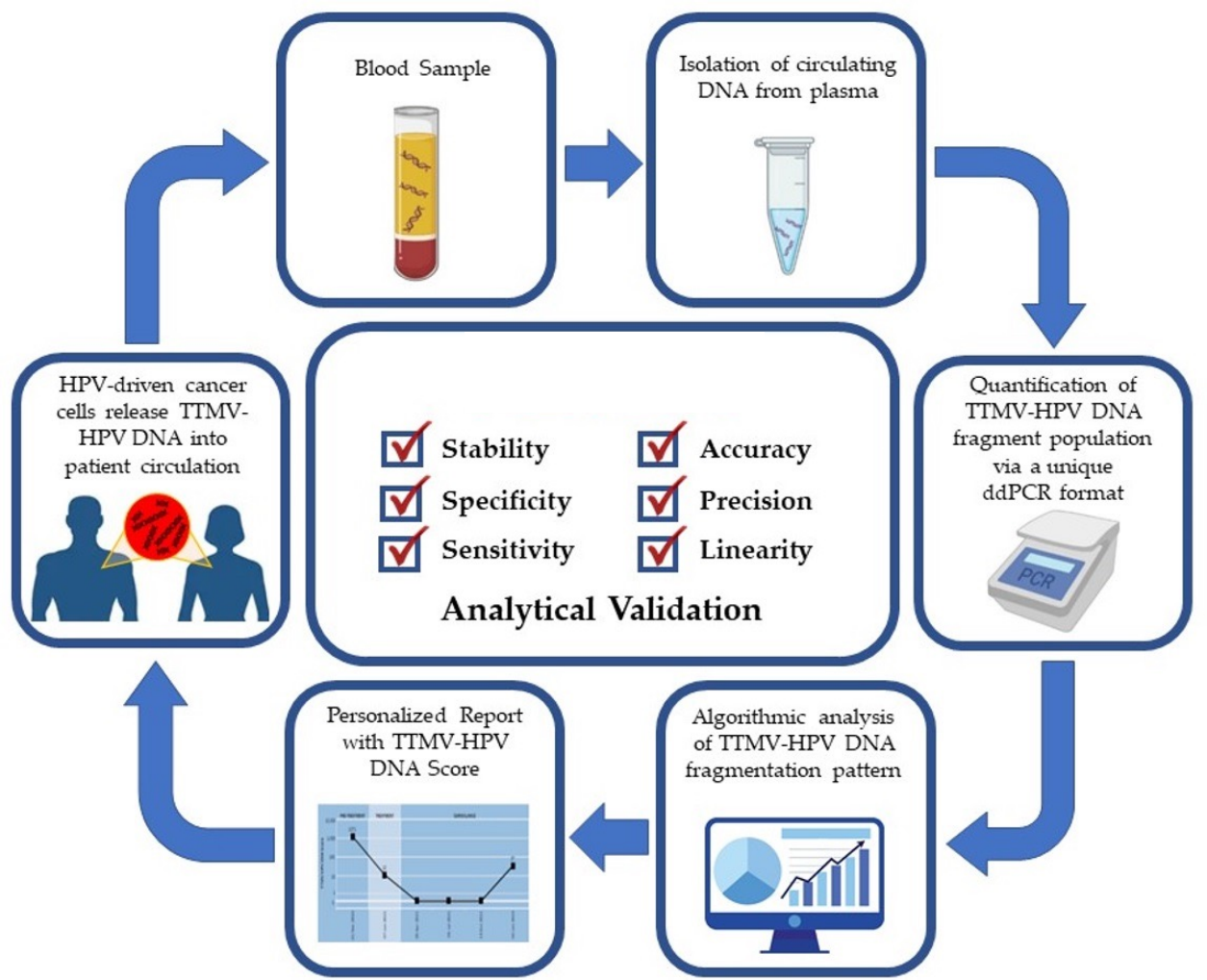
Why are we discussing circulating tumor HPV DNA (ctDNA)?

- HPV-related oropharynx squamous cell carcinoma(OPSCC) generally has a good prognosis with a 5-year overall survival rate of 80%-91% and a recurrence-free survival rate of 78%-90%. However, this still has room for improvement and the toxicity burden from treatment remains high.

- Can pretreatment HPV ctDNA levels be used to risk-stratify patients?
- How should a patient be managed if HPV ctDNA does not completely clear after treatment?
- Do the dynamics of HPV ctDNA clearance during treatment predict the eventual response?
- What should be done in the case of detectable HPV ctDNA without clinically or radiographically evident disease?

Xie et al. JCO 2022
Haring et al. Cancer Cyto 2023

What is HPV ctDNA testing?



There are multiple different tests being developed, with ddPCR being available commercially, but other methods like NGS being explored. Time will prove the victor, but will generally avoid comparisons for this short debate

Gunning et al. Diagnostics 2023

First question, is the test accurate? YES

Metric	Reference	Method	Result	N	Detected	95% C.I.
Sensitivity	Chera, 2019 [34]	OPSCC tissue HPV+ by p16 [1]	89.3%	103	92	
	Rettig, 2022 [38]	OPSCC tissue HPV+ by p16 and/or RNA in situ hybridization (ISH) [2]	89.1%	110	98	
	Routman, 2022 [36]	OPSCC tissue HPV+ by p16 or RNA in situ hybridization (ISH)	88.9%	45	40	
	Chung, 2022 [39]	OPSCC tissue HPV+ by p16	94.6%	37	35	
	Echevarria, 2022 [42]	OPSCC tissue HPV+ by p16	90.9%	33	30	
	Gerndt, 2021 [41]	OPSCC tissue HPV+ by p16	93.5%	46	43	
		Cumulative Sensitivity Data	90.4%	374	338	87.4–93.4
Metric	**Reference**	**Method**	**Result**	**N**	**Detected**	**95% C.I.**
Specificity	Chera, 2019 [34]	Healthy donors, (n = 55) [3] banked blood, non-HPV related malignancy patients (n = 60)	97.4%	115	3	
	Routman, 2022 [36]	OPSCC tissue HPV negative by p16 and/or ISH	100%	7	0	
	Rettig, 2022 [37]	Academic center biobank samples, prospectively continuously curated, with no cancer or HPV related disease matched 10:1 with 10 cases of HPV-driven HNCs (n = 100) confirmed with p16 and/or ISH	100%	100	0	
		Cumulative Specificity Data	98.6%	222	3	97.1–100

NavDx Positive and Negative Predictive Value for the Detection of Patients with Residual and/or Recurrent HPV-Driven OPSCC in the Post-Treatment Surveillance Population.

Metric	Reference	Method	Result	N	Detected	95% C.I.
PPV	Chera 2020 [35]	Biopsy proven recurrent HPV-driven OPSCC [1]	100%	16	16	
	Berger 2022 [40]	Biopsy and/or imaging confirmed recurrent HPV-driven OPSCC [2]	97.5%	80	78	
		Cumulative PPV Data	97.9%	96	94	95.1–100
	Reference	**Method**	**Result**	**N**	**Detected**	**95% C.I.**
NPV	Chera 2020 [35]	Imaging and clinical examination negative for recurrent OPSCC	100%	99	99	
	Berger 2022 [40]	Clinician reported status as "no evidence of disease" [3]	95.4%	1256	1198	
		Cumulative NPV Data	95.7%	1355	1297	94.6–96.8

Gunning et al. Diagnostics 2023

How does this stack up to other standard of care biomarkers?

CEA- Sensitivity of CEA ranged from 17.4 % to 100 %, specificity ranged from 66.1 % to 98.4 %, positive predictive value ranged from 45.8 % to 95.2% and negative predictive value ranged from 74.5 % to 100 % for colon cancer recurrence

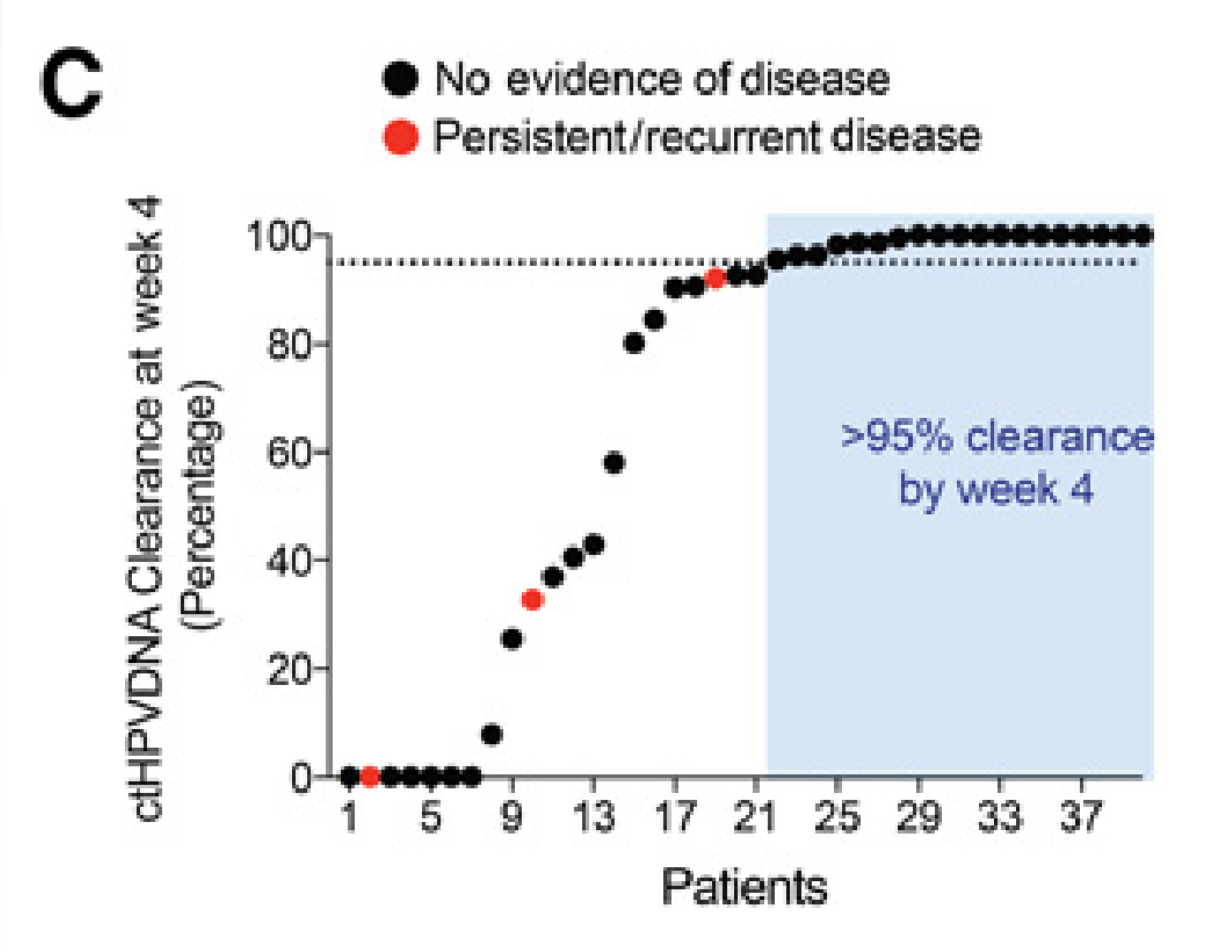
Overall, an elevated **serum CA 19-9** level has a sensitivity of 79-81% and a specificity of 82-90% for diagnosing pancreatic cancer in symptomatic patients

The sensitivity of **CA125** for ovarian cancer in female patients in this population was 88.6%, but with a specificity of only 72.0%

Sorenson et al Int J Surg 2016
Ballehaninna J Gastrointest Oncol 2012
Moss et al J Clin Pathol 2005

Predicting Treatment Response Earlier

- Patients in initial studies had circulating tumor HPV DNA (ctHPVDNA) drawn weekly during CRT
- 67 patients with weekly samples, post-treatment PET, and 16.5 mo median follow-up
- 28% of patients with “favorable” (>95%) clearance by day 28 – none of these patients recurred
- Can we offer individualized RT doses and treatment based on early treatment response?



Chera BS, et al. *Clin Cancer Res*. **2019**.

Negative Predictive Value of HPV CTDNA for OPSCC Surveillance

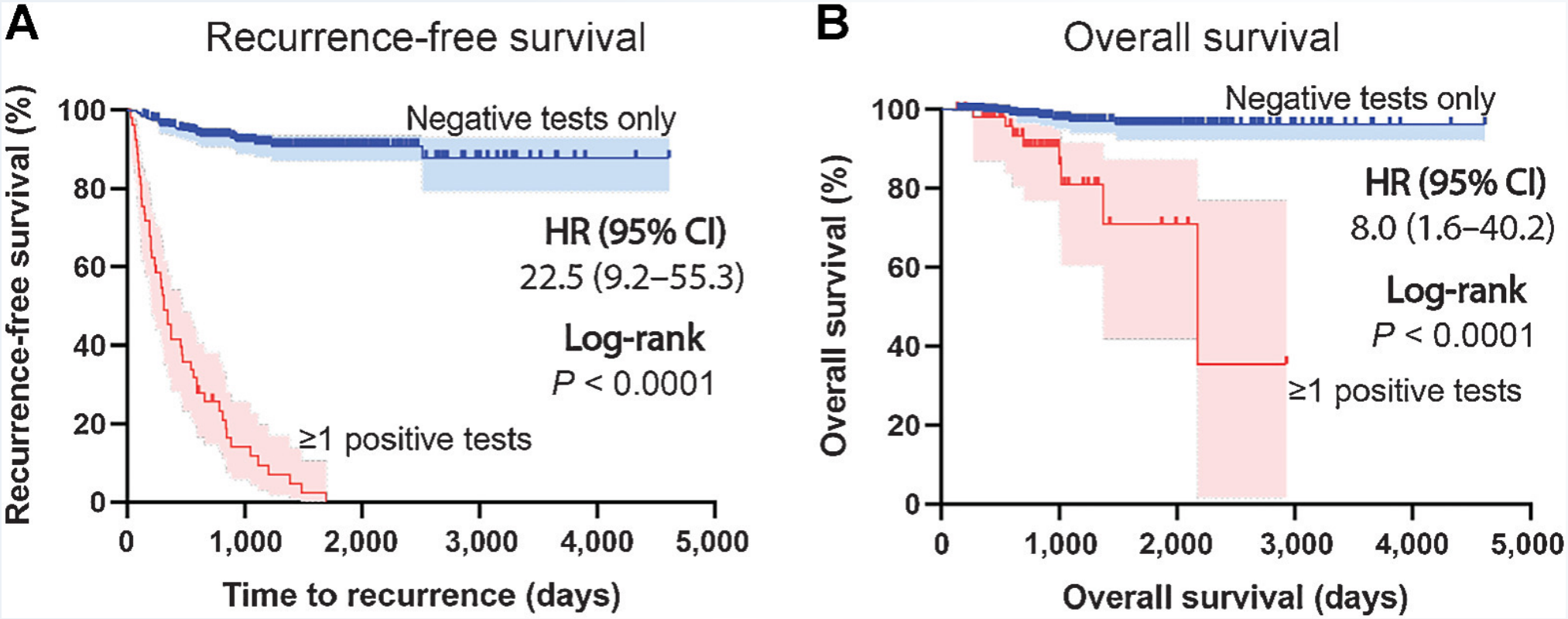
Retrospective Cohort study of 543 HPV related tumors treated with definitive intent therapy across 8 institutions

Must have had ctDNA testing at least 3 months or later from therapy.

Initial treatment modality	
Surgery	121 (22)
Chemoradiation	227 (42)
Surgery + RT	84 (15)
Surgery + chemoradiation	81 (15)
Other (chemotherapy, radiation only, immunotherapy, or EGFR inhibitor)	30 (6)

Hanna et al. CCR 2023

Negative Predictive Value of HPV CTDNA for OPSCC Surveillance



NPV=98.4%!

Hanna et al. CCR 2023

Emory/Vanderbilt Study – Winship-5566

- Powered for 1yr MDADI compared to E3311
- Completely accrued (n = 35)

T1-2, N0-1, M0
HPV-associated oropharyngeal squamous cell carcinoma undergoing TOS

AND

<10 pkyr smoking history or <30 pkyr + quit >5 years ago

AND

Positive pre-treatment ctHPVDNA

→ Intermediate Risk:
pT3, close margin (≤2mm), 2-4 positive nodes (or single node >3 cm), perineural invasion

→ ctHPVDNA

-ve → 36 Gy @ 2.4 Gy/fx adjuvant RT AND omit RT to primary site if ≥2mm margins

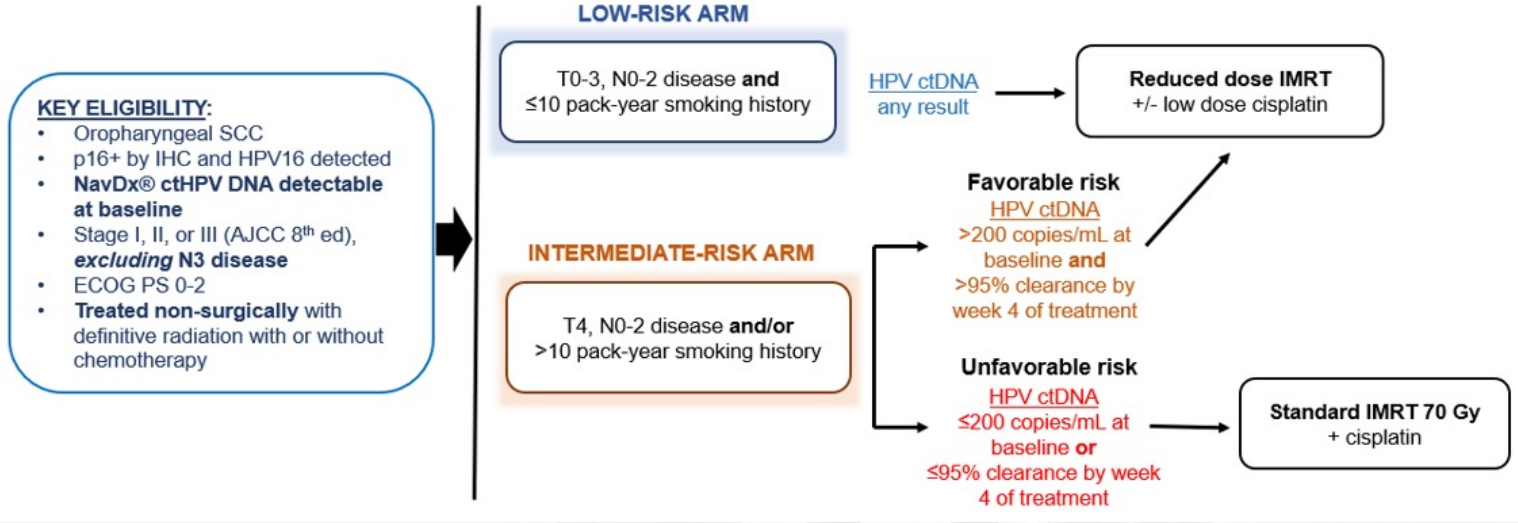
+ve → 50 – 60 Gy @ 2 Gy/fx

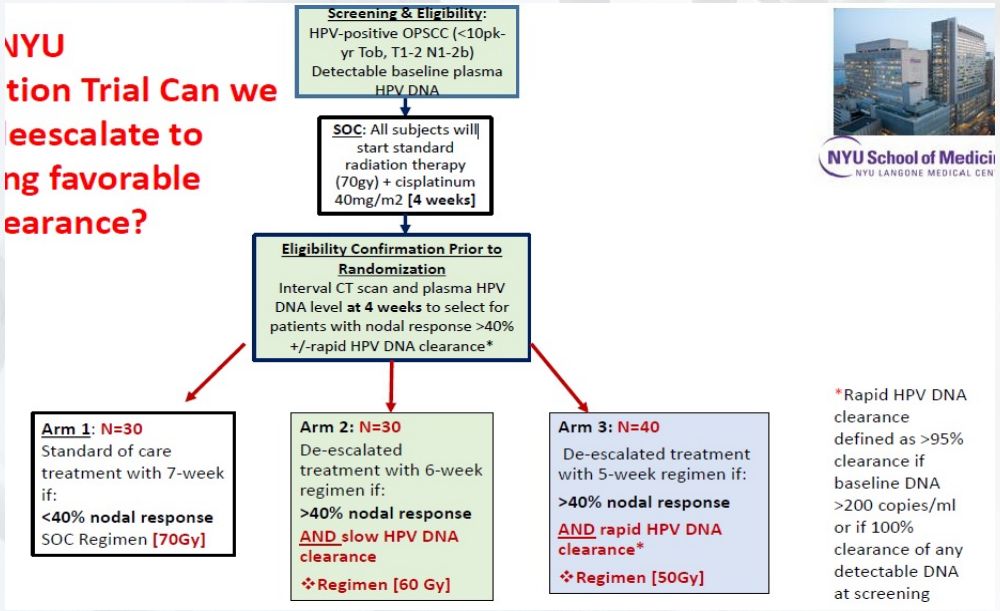
Courtesy of Dr James Bates

Results

- Results: A total of 35 patients have been accrued
- The median age was 57 years (range 33 – 74 years), all (15; 100%) were male, 8 (53%) had T1 disease, all (15; 100%) had N1 disease, and 10 (67%) had base of tongue primary tumors.
- Two patients (13%) had detectable post-operative ctHPVDNA and were treated at discretion of treating radiation oncologist. All other patients (n = 13) had an undetectable post-operative ctHPVDNA and received 36 Gy of adjuvant RT.
- The six-month locoregional control rate is 100%, fulfilling the first interim safety analysis. With a median follow-up of 12.5 mo (range 9.3 – 24.7 mo), there have been no locoregional failures among the first 15 patients.
- Conclusions: Among patients with early-stage HPV-OPSCC undergoing TOS and neck dissection with intermediate-risk pathologic features, ctHPVDNA-guided de-escalation of adjuvant RT does not appear to result in an unacceptable risk of early locoregional recurrence.

Adaptive treatment studies based on ctDNA





Study Schema

- Oropharyngeal squamous cell carcinoma, p16-positive (HPV)
- ≤10 pack-year history of smoking
- Non-metastatic (M0)
- cT0, N1-2; T1-2, N1-2; T3-T4, N0-2 (AJCC 8th edition)
- ≥200 circulating (Tumor Tissue modified viral) TTMV HPV DNA at baseline

Chemo-Radiation delivered for first four weeks. TTMV HPV DNA re-assessed at Week 4 (Treatment 20)

*Favorable TTMV kinetics → Arm 1: 53 Gy in 5 weeks with Chemotherapy

**Unfavorable TTMV kinetics → Arm 2: 69.96 in 7 weeks with Chemotherapy

*Favorable Kinetics defined as a baseline TTMV level of 200 copies/mL and achieve a >95% reduction by week 4 (Treatment 20)

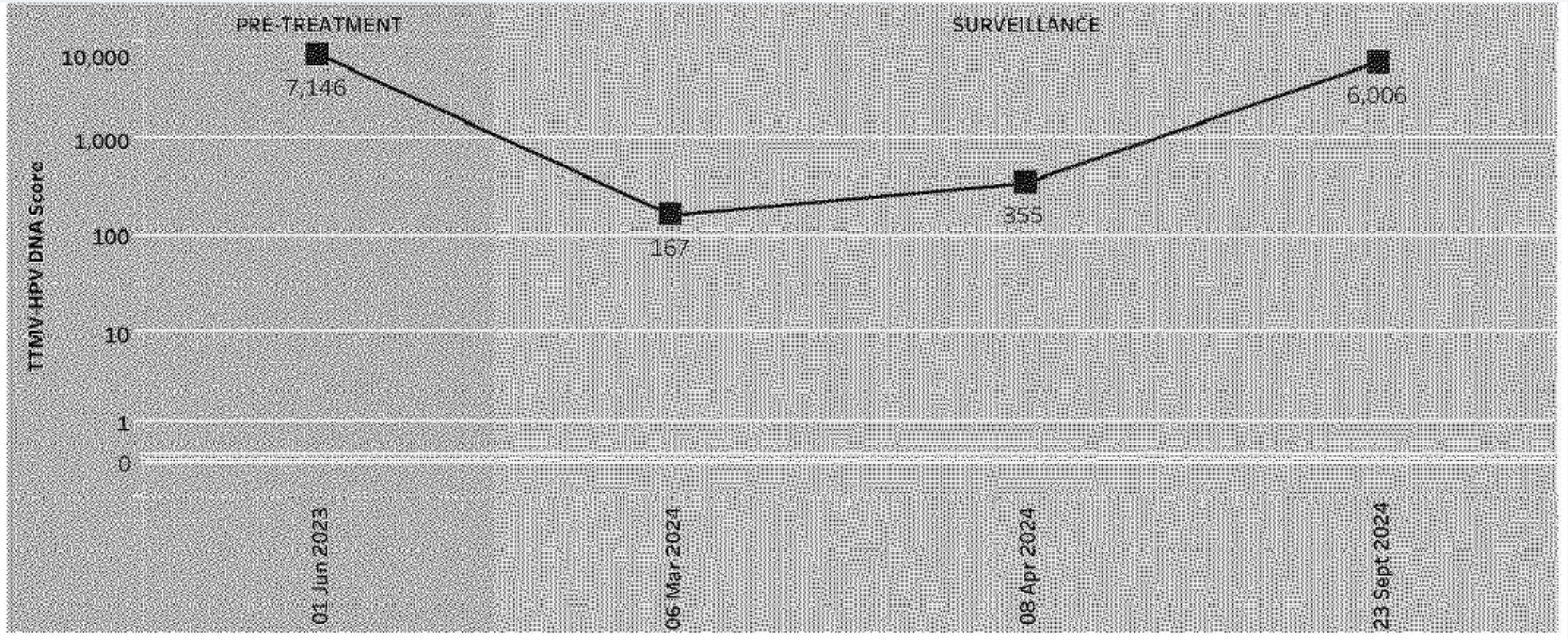
**Unfavorable Kinetics defined as a baseline TTMV level of 200 copies/mL and does not achieve a >95% by week 4 (Treatment 20)

See Section 5 for radiation and systemic therapy details.

Patient Example

- Male with complaints of ear fullness that started in the fall of 2022 and right sided neck fullness in April 2023.
- CT neck wo contrast revealing abnormal right cervical LN levels II-IV and some slight asymmetry along the right GTS.
- Right neck cervical LN 5/15/2023- metastatic squamous cell carcinoma, p16+, PDL-1 and CPS 5-10
- CRT 6/23 with cisplatin, changed to carboplatin and paclitaxel

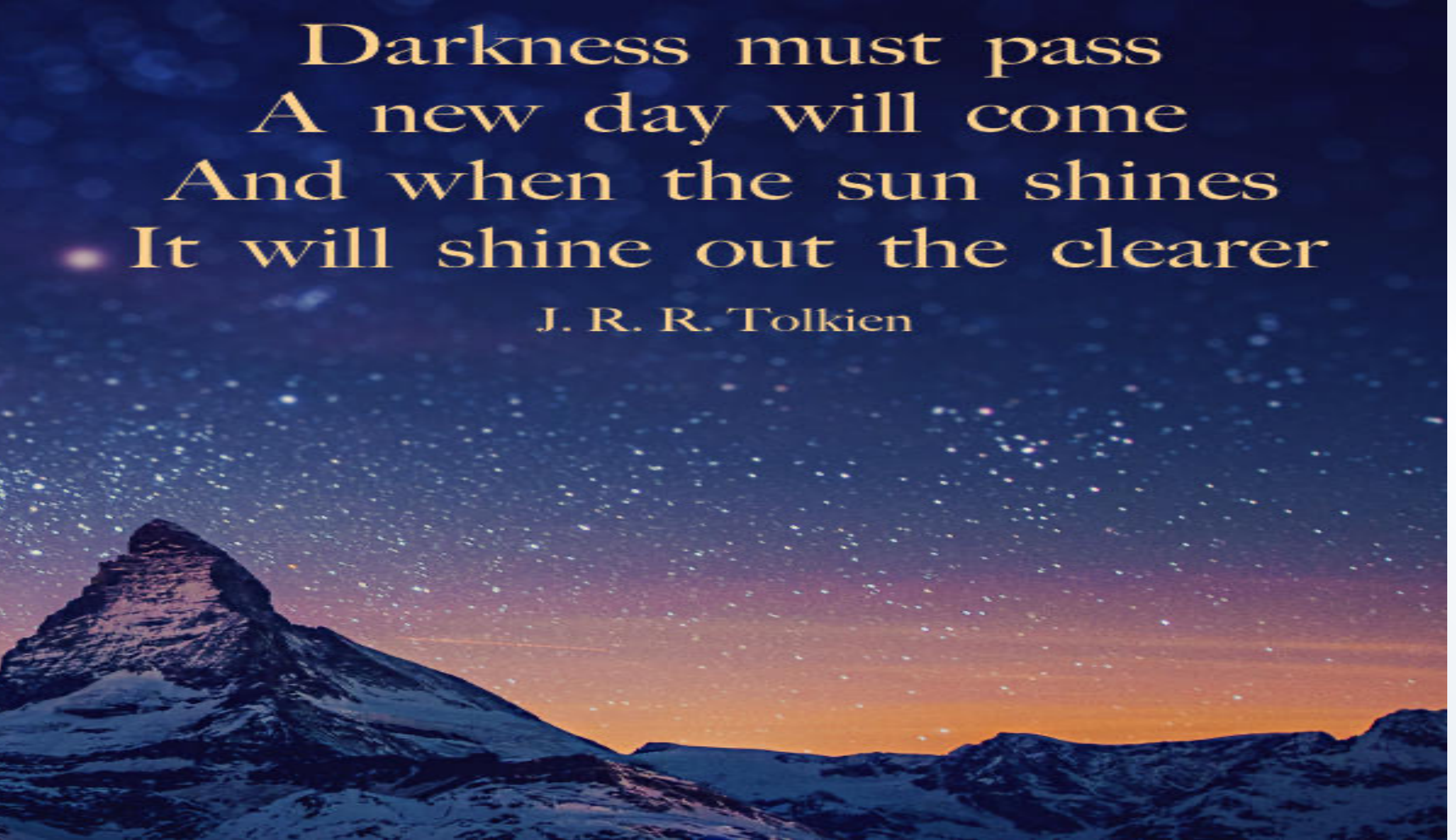
Patient Example



Multiple scans showed no evidence of recurrence, until intrathoracic LN seen 1/25

Conclusions

- More efficacy is needed with less toxicity for HPV related OPSCC
- There are multiple methods of measuring HPV ctDNA, and they are accurate
- They are great at indicating early recurrences, which can either prompt further work up or maybe one day treatment alone
- Good at indicating patients that will do well. Current studies looking to use this to de-escalate select patients (and conversely maybe escalate?)
- Easy! Scans and direct visualizations can be a challenge for patients
- Perhaps ctDNA dynamics can play a role in the metastatic setting, beyond just surveillance


Darkness must pass
A new day will come
And when the sun shines
It will shine out the clearer
J. R. R. Tolkien

Q&A