

HPV Related Oropharyngeal Cancer Update

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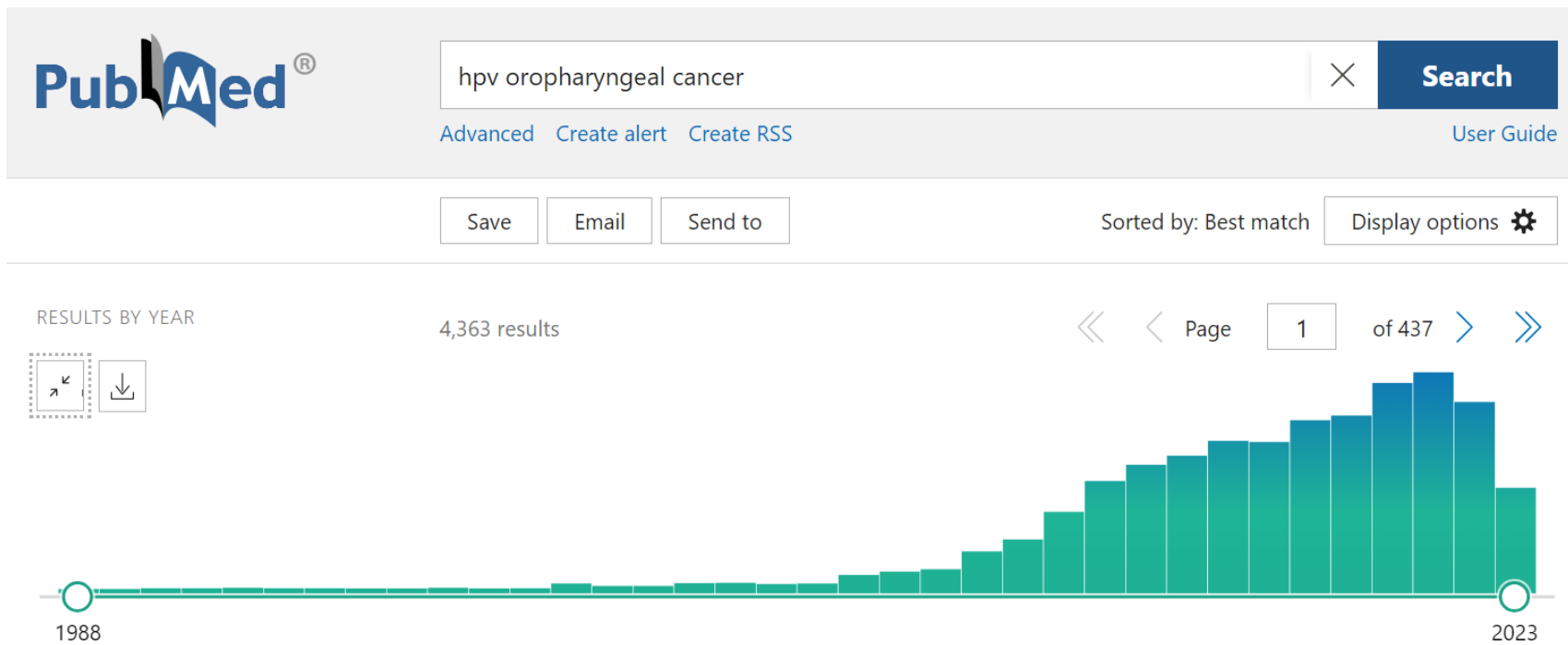
Terry Day, MD, FACS

2023 SCOS Annual Conference

August 4–5th, 2023 | Wild Dunes Resort, Isle of Palms, SC



HPV related Oropharyngeal cancer research



Commonly Asked Questions

- **From patient:**

- I'm scheduled for radical neck dissection and tonsillectomy next week, should I go ahead with that?
- They're putting in my PORT and feeding tube tomorrow but a friend told me that I should have surgery, what should I do?
- Is my HPV contagious? How did I get this? Can I get the vaccine?
- I finished my treatment but now I have lots of mucous and can't swallow or taste. Can you help?

- **From me to the patient: Who is your speech therapist? Who is your dentist?**

- ***From me to the radiation oncologist: What dose to contralateral tonsil, base of tongue, neck, larynx, mandible? Will negative margins or biopsy or lymph nodes reduce that dose? What modality would result in best QOL?***

Social Determinants of Health in OPSCC

JCO® Oncology Practice
An American Society of Clinical Oncology Journal

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PMCID: PMC8258012

PMID: [33434083](https://pubmed.ncbi.nlm.nih.gov/33434083/)

Socioeconomic Factors Influence the Impact of Tumor HPV Status on Outcome of Patients With Oropharyngeal Squamous Cell Carcinoma

Jennifer A. Marks, MD,¹ Jeffrey M. Switchenko, PhD,² Connor E. Steuer, MD,³ Martha Ryan, NP,³ Mihir R. Patel, MD,⁴ Mark W. McDonald, MD,³ Kristin Higgins, MD,³ Johnathan J. Beittler, MD, MBA,^{3,4,5} Dong M. Shin, MD,³ Theresa W. Gillespie, PhD,⁶ and Nabil F. Saba, MD³



JOURNAL OF THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK

ORIGINAL ARTICLE

Social determinants of health and treatment decisions in head and neck cancer

Jennifer N. Shehan MD, Tooba Alwani BA, Jessica LeClair BS, Taylor F. Mahoney MA, Pratima Agarwal MD, Saillit T. Chaudhry BA, Judy J. Wang MSE, Jacob Pieter Noordzij MD, Lauren F. Tracy MD ... See all authors ▾

First published: 10 December 2021 | <https://doi.org/10.1002/hed.26931> | Citations: 1

TABLE 1.

HPV Comparisons

Covariate	Statistics	Level	HPV Status		Parsimonious P-value*
			Negative n (n (%))	Positive n = 11,583	
Race	n (Col %)	White	5,614 (89.31)	10,871 (93.80)	< .001
	n (Col %)	Black	821 (13.48)	526 (4.62)	
	n (Col %)	Others	348 (5.72)	377 (3.33)	
Sex	n (Col %)	Male	5,612 (96.18)	10,883 (97.05)	< .001
	n (Col %)	Female	1,569 (25.96)	1,500 (12.95)	
Clinical T stage	n (Col %)	T1	1,445 (21.96)	3,409 (29.43)	< .001
	n (Col %)	2	2,454 (37.29)	4,995 (43.12)	
	n (Col %)	3	1,454 (22.09)	1,800 (15.42)	
Clinical N stage	n (Col %)	0	1,512 (23.98)	1,414 (12.21)	< .001
	n (Col %)	1	1,144 (17.98)	1,899 (16.39)	
	n (Col %)	2	3,618 (54.98)	7,796 (67.31)	
Treatment	n (Col %)	3	307 (4.66)	474 (4.08)	
	n (Col %)	Surgery first	2,106 (32)	4,568 (39.82)	< .001
	n (Col %)	Chemo or RT first	4,475 (68)	7,075 (61.08)	
Facility location	n (Col %)	Northeast	1,353 (20.56)	2,472 (21.34)	< .001
	n (Col %)	South	2,671 (40.59)	3,827 (33.04)	
	n (Col %)	Midwest	1,621 (24.63)	3,323 (28.69)	
Facility type	n (Col %)	West	936 (14.22)	1,961 (16.93)	
	n (Col %)	Community cancer program or integrated network cancer program	1,280 (19.45)	2,009 (17.34)	< .001
	n (Col %)	Comprehensive community cancer program	2,315 (35.18)	3,836 (33.29)	
Insurance status	n (Col %)	Academic or research program	2,986 (45.37)	5,038 (43.32)	
	n (Col %)	Not insured	485 (7.37)	454 (3.92)	< .001
	n (Col %)	Private	2,959 (44.96)	7,250 (62.79)	
Median income quartiles, 2000	n (Col %)	Medicaid or Medicare or other government	3,137 (47.67)	3,879 (33.49)	
	n (Col %)	< \$30,000	1,033 (15.7)	1,061 (9.16)	< .001
	n (Col %)	\$30,000-\$34,999	1,389 (20.7)	1,781 (15.38)	
Percent of no high-school education quartiles, 2000	n (Col %)	\$35,000-\$49,999	1,865 (28.36)	3,253 (28.08)	
	n (Col %)	\$45,000+	2,514 (38.2)	3,488 (30.18)	
	n (Col %)	> 20%	1,174 (17.86)	1,312 (11.33)	< .001
Urban or rural, 2000	n (Col %)	20%-28.9%	1,595 (24.26)	2,436 (21.03)	
	n (Col %)	18%-19.9%	1,611 (24.48)	2,962 (25.71)	
	n (Col %)	< 14%	2,291 (34.48)	4,973 (42.93)	
Great circle distance	n (Col %)	Metros	5,488 (83.26)	9,622 (83.07)	.423
	n (Col %)	Urban	983 (14.94)	1,736 (14.99)	
	n (Col %)	Rural	330 (5.07)	225 (1.94)	
Age at diagnosis	n (Col %)	< 10 miles	3,273 (49.73)	4,656 (40.2)	< .001
	n (Col %)	10-50 miles	2,650 (39.4)	3,147 (27.44)	
	n (Col %)	> 50 miles	715 (10.86)	1,780 (15.37)	
Mean	n	6,581	11,583	< .001	
	Median	60.29	58.62		
	Median	59	58		

Abbreviations: ANOVA, analysis of variance; HPV, human papilloma virus; RT, radiation therapy.
*The p-value for Positive is calculated by ANOVA for numerical covariates and chi-square test for categorical covariates.

TABLE 2. Multivariate Analysis: Overall survival by HPV-Positive

Covariate	Level	Overall Survival (Years from Diagnosis)	
		Hazard Ratio	HR P-Value
Race	Others	0.58 (0.36-0.92)	.022
	Black	1.02 (0.83-1.25)	.884
	White	—	—
Sex	Male	1.12 (0.97-1.30)	.126
	Female	—	—
Age at diagnosis	1.00 (1.00-1.00)	< .001	
	3.47 (2.94-4.09)	< .001	
Clinical T stage	4	2.31 (1.96-2.72)	< .001
	2	1.46 (1.26-1.68)	< .001
	0/1	—	—
Clinical N stage	0/1	2.10 (1.68-2.64)	< .001
	2	1.17 (1.00-1.37)	.047
	1	0.83 (0.68-1.02)	.077
Treatment	Chemo or RT first	1.34 (1.18-1.51)	< .001
	Surgery first	—	—
	0	—	—
Facility location	Northwest	0.87 (0.74-1.02)	.078
	South	0.83 (0.72-0.96)	.013
	Midwest	0.93 (0.80-1.07)	.306
	West	—	—
Facility type	Community cancer program or integrated network cancer program	1.02 (0.88-1.17)	.793
	Comprehensive community cancer program	1.15 (1.02-1.29)	.023
	Academic or research program	—	—
Insurance status	Medicaid or Medicare or other government	0.97 (0.78-1.21)	.792
	Private	0.51 (0.41-0.63)	< .001
	Not insured	—	—
Median income quartiles, 2000	< \$30,000	1.42 (1.15-1.76)	< .001
	\$30,000-\$34,999	1.23 (1.04-1.47)	.019
	\$35,000-\$49,999	1.21 (1.05-1.39)	.007
	\$46,000+	—	—
Percent of no high-school education quartiles, 2000	> 20%	1.28 (1.00-1.62)	.028
	20%-28.9%	1.06 (0.90-1.24)	.494
	14%-19.9%	1.07 (0.93-1.22)	.376
Urban or rural, 2000	Rural	1.21 (0.88-1.65)	.245
	Urban	0.94 (0.81-1.10)	.468
	Metros	—	—
Great circle distance	> 50 miles	0.83 (0.70-0.98)	.031
	10-50 miles	0.87 (0.78-0.98)	.018
	< 10 miles	—	—

NOTE. Number of observations in the original data set = 11,583. Number of observations used = 11,583.
Abbreviations: HPV, human papilloma virus; HR, hazard ratio.

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Objectives

- Discuss the current guideline-based management of HPV+ OPSCC
- Review common pre-treatment multidisciplinary considerations
- Prepare for evidence-based answers to frequent questions that patients ask when newly diagnosed
- Understand the approach to consideration of surgical treatment options
- Analyze the role of liquid biopsy or ctDNA in OPSCC
- Recognize why long-term surveillance and survivorship is different for OPSCC patients than other patients with lung or breast or prostate cancers

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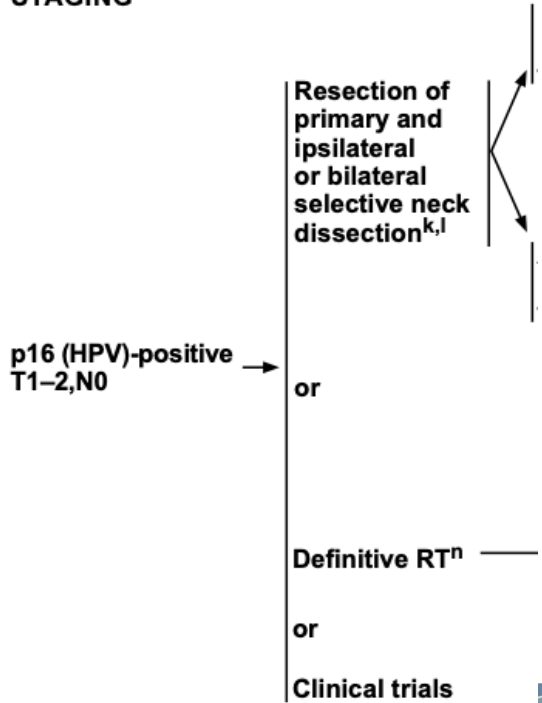
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HPV+ OPSCC Guidelines Early Stage

Base of Tongue/Tonsil/Posterior Pharynx:
CLINICAL STAGING TREATMENT OF PI

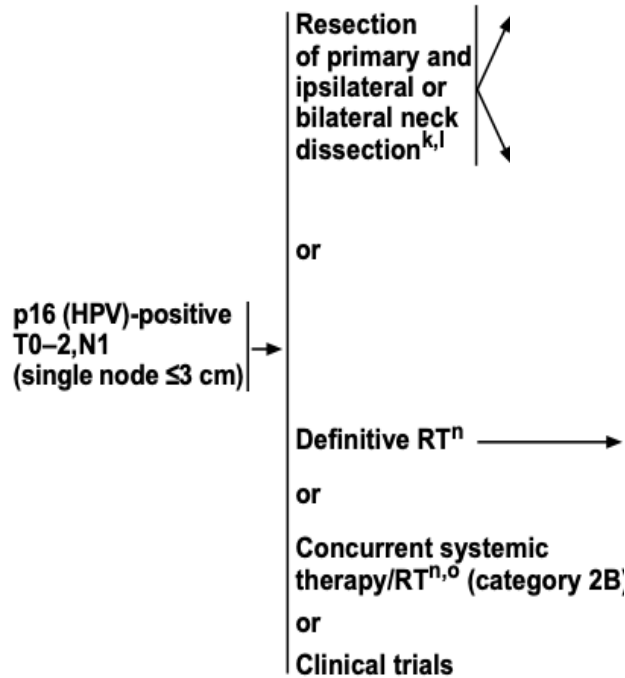
- Surgery or RT



HPV+ OPSCC Guidelines Intermediate Stage

Base of Tongue/Tonsil/Posterior Pharyngeal Wall/Soft Palate
CLINICAL STAGING^j TREATMENT OF PRIMARY AND NECK

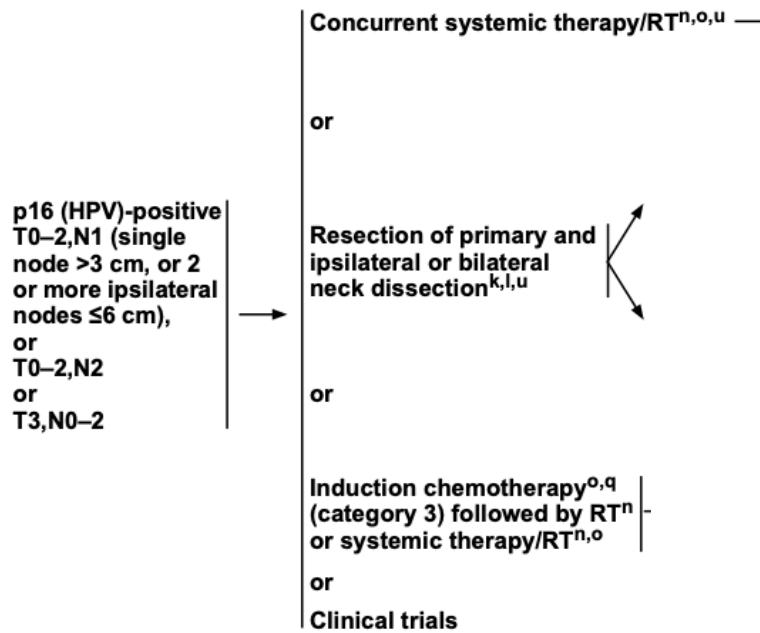
- Surgery or RT



HPV+ OPSCC Guidelines Late Stage

Base of Tongue/Tonsil/Posterior Pharyngeal Wall/Soft Palate
CLINICAL STAGING^j TREATMENT OF PRIMARY AND NECK

- Surgery or RT



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Pre-Treatment Considerations



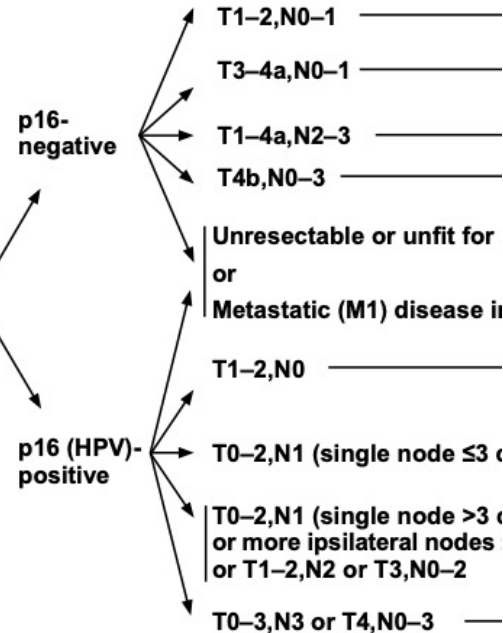
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NCCN Guidelines Version 2.2023 Cancer of the Oropharynx

Base of Tongue/Tonsil/Posterior Pharyngeal Wall/Soft Palate WORKUP

- Tumor human papillomavirus (HPV) testing by p16 immunohistochemistry (IHC) required^a
- H&P^{b,c} including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy of primary site or fine-needle aspiration (FNA) of the neck^d
- CT with contrast and/or MRI with contrast of primary and neck^e
- As clinically indicated:
 - ▶ EUA with endoscopy^f
 - ▶ Preanesthesia studies
 - ▶ FDG-PET/CT^e
 - ▶ Chest CT^e (with or without contrast)
 - ▶ Dental evaluation^g including Panorex
 - ▶ Nutrition, speech and swallowing evaluation/therapy, and audiogram^h
 - ▶ Smoking cessation counseling^b
 - ▶ Fertility/reproductive counselingⁱ
- Multidisciplinary consultation as clinically indicated

CLINICAL STAGING^j



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Commonly Asked Questions

- **From patient:**

- Is my HPV contagious? How did I get this? Is my partner at risk? Can I get the vaccine?
- I'm scheduled for radical neck dissection and tonsillectomy next week, should I go ahead with that?
- They're putting in my PORT and feeding tube tomorrow but a friend told me that I should have surgery, what should I do?
- I finished my treatment but now I have lots of mucous and can't swallow or taste. Can you help?

- **From me to the patient: Who is your speech therapist? Who is your dentist?**

- ***From me to the radiation oncologist: What dose to contralateral tonsil, base of tongue, neck, larynx, mandible? Will negative margins or biopsy or lymph nodes reduce that dose?***

Review

Is there an increased risk of cancer among spouses of patients with an HPV-related cancer: A systematic review

Haitham Mirghani^a  , Erich M. Sturgis^b, Anne Aupérin^c, Joseph Monsonego^d,
Pierre Blanchard^e

- 53 studies met inclusion criteria
- Coincidence of HPV induced cancer in couples
 - 13 case reports/series, 9 population registries
 - 4 showed cervical cancer in partner
 - 1 showed increase of OPSCC in partner
- Of the 4 positive studies, OR of 2.6 to 6.7
- Overall absolute risk of 1-3%

Who's at Risk of OPSCC?

article

Annals of Oncology



ORIGINAL ARTICLE

Annals of Oncology 28: 3065–3069, 2017
doi:10.1093/annonc/mdx535
Published online 19 October 2017

Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer

G. D'Souza¹, T. S. McNeel² & C. Fakhry^{3*}



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HPV Roundtable

You have the power to reduce the incidence of human papillomavirus (HPV) cancers and pre-cancers among patients in your care. HPV cancer prevention starts with you.

Oral health professionals play a critical role in combating growing rates of HPV-positive oropharyngeal cancers, which affect the tonsils and the base of the tongue. Oral health professionals should strongly and clearly recommend HPV vaccination to all age-eligible patients.

The Problem

HPV-positive oropharyngeal cancer has surpassed cervical cancer as the most prevalent HPV cancer. Certain strains of HPV cause 70% of oropharyngeal cancers in the U.S., affecting about 13,500 people each year. One in nine American men have oral HPV, and cancers of the oropharynx are about four times more common in men than women.¹ Oral HPV has been detected in newborns when the mother has an HPV cervical infection,² and research shows that 2.5% of adolescents have HPV.³ Although most cases of HPV resolve without incident, HPV causes about 34,800 cases of cancer in men and women each year in the U.S., including cancers in the oropharynx, cervix, vagina, vulva, penis, and anus.⁴

The Solution

The HPV vaccine is cancer prevention. Boys and girls should get the HPV vaccine series at age 11 or 12. The vaccine can be given starting as early as age 9. The HPV vaccine is most effective when given before age 13 to achieve the best immune response, and it provides long-lasting protection.⁵ For patients who were not vaccinated on time at 11-12, vaccination may be provided up to age 26 for females and males.

HPV vaccination works. The HPV vaccine prevents infection by the HPV types that cause the vast majority of HPV cancers and genital warts. In fact, infections with the HPV types that cause most HPV cancers and genital warts have dropped 71% among teen girls since children first started getting the vaccine in 2006.⁶

HPV is linked with:

70% of oropharynx
91% of cervical and anal cancers
63% of penile cancers⁷

71% ↓ drop in HPV infections among teen girls since 2006

High-Risk Factors for Oropharyngeal Cancer^{8,9}

- Chewing tobacco
- Heavy smoking (more than a pack a day)
- Chronic inflammation
- Having a weakened immune system
- Poor oral hygiene
- Current marijuana use
- Having 16 or more lifetime vaginal or oral sex partners
- Men with two or more same-sex oral sex partners

It is estimated that approximately 90% of the newly diagnosed HPV-attributable cancers in the United States could be prevented by receipt of the HPV vaccine,¹⁰ and there is evidence that the vaccine may help prevent oral HPV infections.¹¹ [Get more facts.](#)²

Educate patients and parents of age-eligible children about the link between HPV and oropharyngeal cancers, and advocate for HPV vaccination as cancer prevention. With the annual number of oropharyngeal cancers on the rise, dental providers play an important role in educating their patients about ways to prevent this type of cancer. You and your colleagues should understand and encourage HPV vaccination. On the pages that follow, you will find a list of actionable steps you can take to reduce the burden of HPV cancers within your community today.

<http://hpvroundtable.org/wp-content/uploads/2018/04/DENTAL-Action-Guide-WEB.pdf>



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Gardasil 9 HPV Vaccine

- Indicated in **girls and women 9 through 45 years of age** for the prevention of the following diseases:
 - Cervical, vulvar, vaginal, anal, **oropharyngeal and other head and neck** cancers caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58.
- Indicated in **boys and men 9 through 45 years of age** for the prevention of the following diseases:
 - Anal, **oropharyngeal and other head and neck cancers** caused by HPV types 16, 18, 31, 33, 45, 52, and 58.

<https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9>

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Diagnosis

- Often diagnosis at advanced stage
- Symptoms – dysphagia, odynophagia, referred otalgia, sore throat
- Common presenting symptom – a neck mass
- Diagnosis is tissue-based
 - Primary-site biopsy, consider tonsillectomy if primary is occult
 - Fine needle aspiration (FNA)/biopsy of a regional lymph node – **FNA is preferred**
 - p16+ is strongly associated with oropharyngeal SCC

Small primary lesion (T1)

Base of tongue



Left tonsil



Large primary tumor (T2)

- The tumor involves the right base of tongue, tonsil, right lateral pharyngeal wall and extending to soft palate past midline



Transoral robotic surgery for oropharyngeal squamous cell carcinoma in the era of human papillomavirus

Omar Mahmoud^{1 2}, Kim Sung^{1 2}, Francisco J Civantos³, Giovanna R Thomas³, Michael A Samuels⁴

radiotherapy. The overall survival (OS) was compared by treatment strategy, including propensity matching to control for confounders.

Results: Of 1873 patients, 73% were HPV-positive and 30% were treated with TORS. The propensity-matched patients with HPV-positive disease displayed no significant difference in 3-year survival; 95% versus 91% ($P = .116$) for the TORS versus primary radiotherapy. In the HPV-negative cohort, TORS was associated with superior survival; 84% versus 66% ($P = .01$).

Conclusion: The TORS-based approach was associated with superior survival in patients with HPV-negative oropharyngeal SCC; similar difference was not observed in patients with HPV-positive disease.

- Deintensification is warranted in patients with HPV+ OPSCC (survival rates exceeding 90%)
- The opposite is true for HPV-negative OPSCC, in which intensification may improve their poor prognosis.

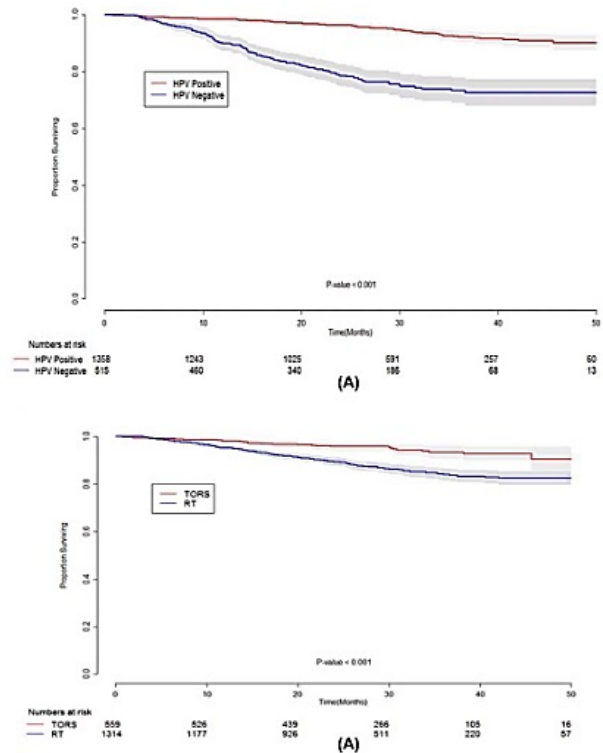


FIGURE 2 Overall survival curves by A, human papillomavirus (HPV) status and B, treatment subgroups. RT, radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

TORS for occult primary

- Presented with left neck mass at level II-III
- FNA – SCC, p16+
- Physical examination - Left tonsil erythema and mild increased fullness. Base of tongue mild asymmetry, with increased fullness on the left
- PET-CT – subtle uptake at left base of tongue
- TORS

- A. LEFT TONSIL, TONSILLECTOMY:
BENIGN TONSILLAR TISSUE. NO EVIDENCE OF MALIGNANCY.
- B. LEFT BASE OF TONGUE, EXCISION:
- SMALL FOCUS OF INVASIVE SQUAMOUS CELL CARCINOMA (P16+, p63+, ki-67-markedly increased) ARISING FROM LINGUAL TONSILAR TISSUE.
- INVASIVE CARCINOMA INVOLVES THE POSTERIOR TIP MARGIN.
- C. LEFT LEVEL 2 NECK DISSECTION:
- ONE OF SIXTEEN LYMPH NODES POSITIVE FOR METASTATIC SQUAMOUS CELL CARCINOMA (1/16).
- DEPOSIT MEASURES APPROXIMATELY 15 MM IN GREATEST DIMENSION.
- BENIGN PARATHYROID TISSUE PRESENT.
- D. LEFT LEVEL 3 NECK DISSECTION:
EIGHT BENIGN LYMPH NODES (0/8).
- E. LEFT LEVEL 4 NECK DISSECTION:
FOUR BENIGN LYMPH NODES (0/4).

Oncological outcome following de-intensification of treatment for stage I and II HPV negative oropharyngeal cancers with transoral robotic surgery (TORS): A prospective trial



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ABSTRACT

Objective: This prospective study aimed to see long-term oncological outcome of Transoral Robotic Surgery as single modality treatment for cT1-T2 N0 HPV negative oropharyngeal malignancies.

Method: From March 2013 to October 2015, 57 patients with early stage oropharyngeal carcinoma underwent Transoral robotic surgery (TORS) with neck dissection using daVinci® Surgical system. Patients were evaluated for disease free survival, overall survival, locoregional and distant metastasis.

Results: 57 patients (48 males and 9 females) underwent TORS for early stage oropharyngeal carcinoma. All patients underwent ipsilateral neck dissection and 12 patients underwent bilateral neck dissection. 49 patients with final histopathology suggestive of stage I and II disease did not received any adjuvant treatment. Mean age at presentation was 59.4 years (37–88 years). Most common site of involvement was the base of tongue (BOT) in 31 (54.8%) patients. Twenty-four (42.1%) patients were cT1 and 33 (57.9%) were cT2 at presentation. During follow-up, 2 (4.2%) patients recurred locoregionally and 1 (2.1%) patient had distant metastasis. Two patients expired due to causes other than malignancy. Forty-three (89.6%) patients were disease free on an average follow-up of 29 months with an overall survival of 93.8% at mean follow-up of 29 months.

Conclusion: Transoral Robotic Surgery as a single modality treatment is a good option for cure in HPV negative early resectable oropharyngeal malignancies which are relatively unresponsive to radiation. TORS can be used to de-intensify the treatment of early stage oropharyngeal carcinoma and thus avoid the early and late toxicities associated with Radiotherapy/Chemoradiotherapy.

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Differences in Functional and Survival Outcomes Between Patients Receiving Primary Surgery vs Chemoradiation Therapy for Treatment of T1-T2 Oropharyngeal Squamous Cell Carcinoma

Dev R. Amin, MD; Ramez Philips, MD; Dylan G. Bertoni, MD, MS; Eric V. Mastrodonardo, MD; Daniel J. Campbell, MD; Aarti M. Agarwal, MD; Sruti Tekumalla, BS; Zachary D. Urdang, MD, PhD; Adam J. Luginbuhl, MD; David M. Coggnetti, MD; Joseph M. Curry, MD

RESULTS Propensity score matching allowed a study sample with 2 cohorts comprising statistically similar parameters with 363 (50%) patients in each. Patients in the TORS cohort had a mean (SD) age of 68.5 (9.9) vs 68.8 (9.7) years in RT/CRT cohort; 86% and 88% were White individuals, respectively; 79% of patients were men in both cohorts. Primary TORS was associated with clinically meaningful increased risk of dysphagia at 6 months (OR, 1.37; 95% CI, 1.01-1.84) and 1 year posttreatment (OR, 1.71; 95% CI, 1.22-2.39) compared with primary RT/CRT. Patients receiving surgery were less likely to be gastrostomy tube dependent at 6 months (OR, 0.46; 95% CI, 0.21-1.00) and 5 years posttreatment (risk difference, -0.05; 95% CI, -0.07 to -0.02). Differences in overall rates of tracheostomy dependence (OR, 0.97; 95% CI, 0.51-1.82) between groups were not clinically meaningful. Patients with OPSCC, unmatched for cancer stage or human papillomavirus status, who received RT/CRT had worse 5-year overall survival than those who underwent primary surgery (70.2% vs 58.4%; hazard ratio, 0.56; 95% CI, 0.40-0.79).

CONCLUSIONS AND RELEVANCE This national multicenter cohort study of patients undergoing primary TORS vs primary RT/CRT for T1-T2 OPSCC found that primary TORS was associated with a clinically meaningful increased risk of short-term dysphagia. Patients treated with primary RT/CRT had an increased risk of short- and long-term gastrostomy tube dependence and worse 5-year overall survival than those who underwent surgery.

Trans oral robotic surgery for oropharyngeal cancer: A multi institutional experience

Armando De Virgilio ^{a,b,1,*}, Raul Pellini ^{c,1,*}, Giovanni Cammaroto ^d, Rossella Sgarzani ^e, Andrea De Vito ^d, Manlio Gessaroli ^f, Andrea Costantino ^{a,b}, Gerardo Petruzzi ^c, Bianca Maria Festa ^{a,b}, Flaminia Campo ^c, Claudio Moretti ^{c,g}, Barbara Pichi ^c, Giuseppe Mercante ^{a,b}, Giuseppe Spriano ^{a,b}, Claudio Vicini ^{d,g}, Giuseppe Meccariello ^d

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^e Plastic Surgery, DIMES Department, University of Bologna, Bologna, Italy

^f Maxillo-Facial Unit, Department of Surgery, Maurizio Bufalini Hospital, Azienda USL della Romagna, Cesena, Italy

^g University of Ferrara, Ferrara, Italy

- TORS is useful in the management of selected cases of OPSCC
- To limit the treatment at the sole surgical approach or to de-intensify adjuvant treatments

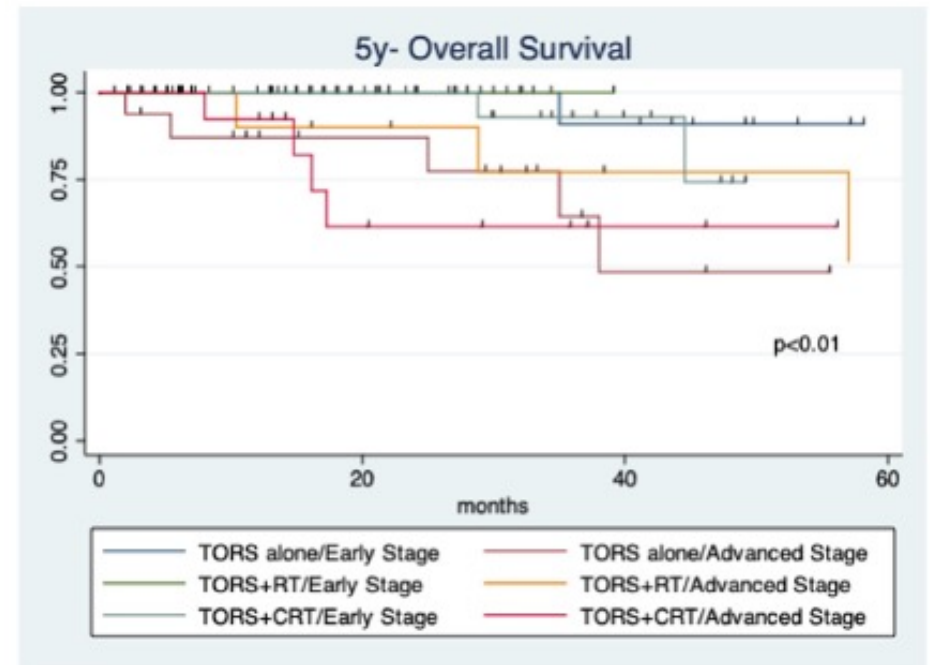


Fig. 1. The 5 year- Overall Survival rate among patients who underwent TORS with or without adjuvants treatments in early and advanced stages according to AJCC 8th edition.

RESEARCH ARTICLE

Open Access



Chemoradiotherapy versus surgery followed by postoperative radiotherapy in tonsil cancer: Korean Radiation Oncology Group (KROG) study

Sanghyuk Song¹, Hong-Gyun Wu^{2*}, Chang Geol Lee³, Ki Chang Keum³, Mi Sun Kim³, Yong Chan Ahn⁴, Dongryul Oh⁴, Hyo Jung Park⁴, Sang-Wook Lee⁵, Geumju Park⁵, Sung Ho Moon⁶, Kwan Ho Cho⁶, Yeon-Sil Kim⁷, Yongkyun Won⁷, Young-Taek Oh⁸, Won-Taek Kim⁹ and Jae-Uk Jeong¹⁰

- 586 patients from 16 hospitals
- No significant difference between the two treatment modalities

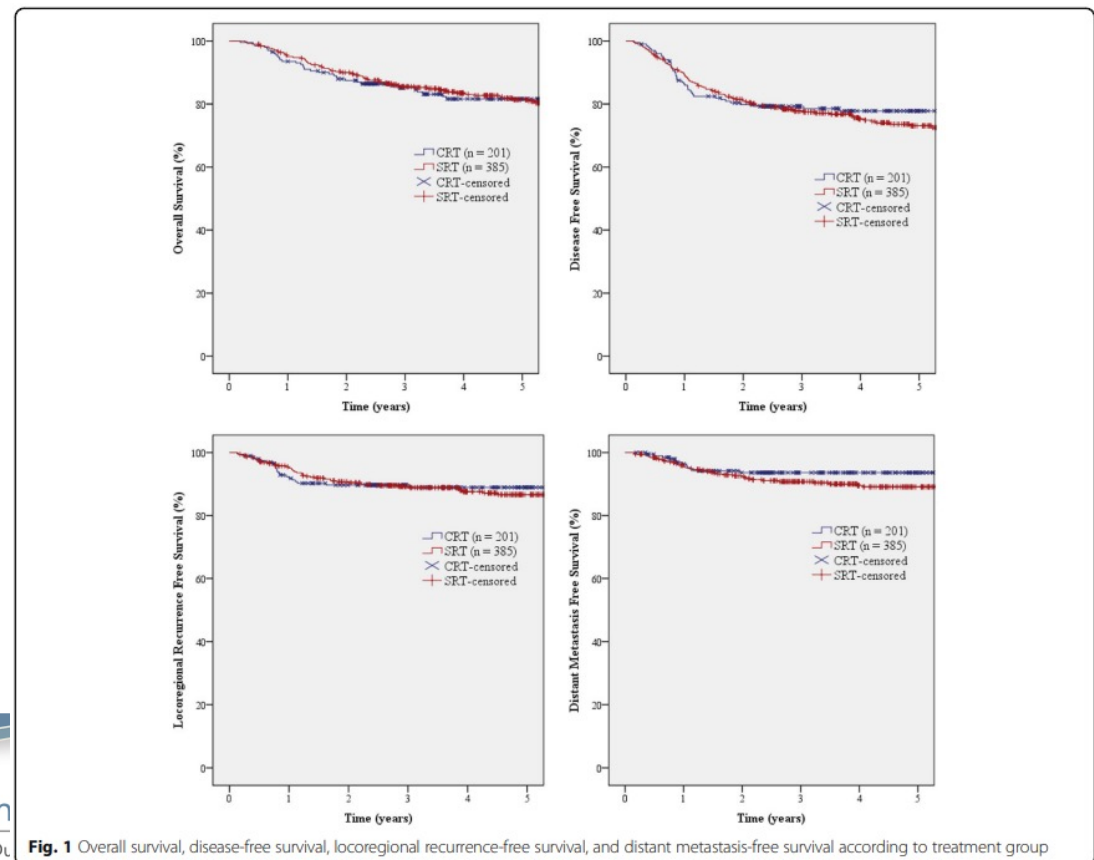


Fig. 1 Overall survival, disease-free survival, locoregional recurrence-free survival, and distant metastasis-free survival according to treatment group

Failure of chemoradiation

- Originally cT2N1, p16 positive
- 4 months after completion of chemoradiation – ulceration of left base of tongue, left pharyngeal wall and fixation of left hemilarynx
- Needs an extensive salvage surgery



Salvage surgery with free flap ALT reconstruction



- Right Composite Resection of mandible, floor of mouth and tongue
- Right Oropharyngectomy with Soft Palate resection
- Right Infratemporal Fossa/Parapharyngeal Space Resection
- Right Pterygomaxillary Fossa Resection
- Neck Dissection

1 year post-op



Review

De-Escalation Strategies for Human Papillomavirus-Associated Oropharyngeal Squamous Cell Carcinoma—Where Are We Now?

Jennifer A. Silver ^{1,2}, Sena Turkdogan ^{1,2}, Catherine F. Roy ^{1,2}, Thavakumar Subramaniam ^{1,2},
Melissa Henry ^{2,3,4,5} and Nader Sadeghi ^{1,2,6,*}

- HPV-related OPSCC is a topic of great interest given the favorable survival outcomes, the need to personalize the treatment and improve quality of life and functional outcomes
- Strategies for de-escalation: surgery and risk-based adjuvant treatment, altered regimen CRT, neoadjuvant chemotherapy with surgical consolidation, and neoadjuvant chemotherapy with risk-based RT consolidation
- A main study - E3311 - the major advantage was for the intermediate-risk category (2-4 lymph nodes without ENE), **no difference** in oncological outcomes with **50 Gy RT instead of 60 Gy**. (359 patients enrolled, **31% received tri-modality therapy**)
- MC1273 trial (upfront surgery with concurrent CRT may allow major **RT dose de-escalation to 30–36 Gy**. Although tri-modality therapy, the reduced-dose adjuvant RT is more likely to spare salivary gland function)

Utility of up-front transoral robotic surgery in tailoring adjuvant therapy

Neil Gildener–Leapman, MD¹, Jeehong Kim, BS², Shira Abberbock, MS³, Garret W. Choby, MD⁴, Rajarsi Mandal, MD⁴, Umamaheswar Duvvuri, MD, PhD^{4,5}, Robert L. Ferris, MD, PhD⁴, and Seungwon Kim, MD^{4,*}

Background—The purpose of this study was to describe how the up-front transoral robotic surgery (TORS) approach could be used to individually tailor adjuvant therapy based on surgical pathology.

Methods—Between January 2009 and December 2013, 76 patients received TORS for oropharyngeal squamous cell carcinoma (OPSCC). Clinical predictors of adjuvant therapy were analyzed and comparisons were made between recommended treatment guidelines for up-front surgery versus definitive nonsurgical approaches.

Results—Advanced N classification, human papillomavirus (HPV)-positive tumor, extracapsular spread (ECS; 26 of 76), perineural invasion (PNI; 14 of 76), and positive margins (7 of 76) were significant predictors of adjuvant chemoradiotherapy (CRT) ($p < .05$). Up-front TORS deintensified adjuvant therapy: 76% of stage I/II and 46% of stage III/IV patients avoided CRT. Conversely, pathologic staging resulted in 33% of patients who would have received radiotherapy (RT) alone based on clinical staging, to be intensified to receive adjuvant CRT.

Conclusion—The TORS approach deintensifies adjuvant therapy and provides valuable pathologic information to intensify treatment in select patients. TORS may be less effective in deintensification of adjuvant therapy in patients with clinically advanced N classification disease.

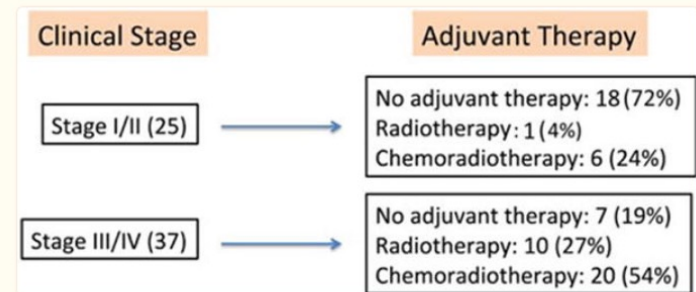


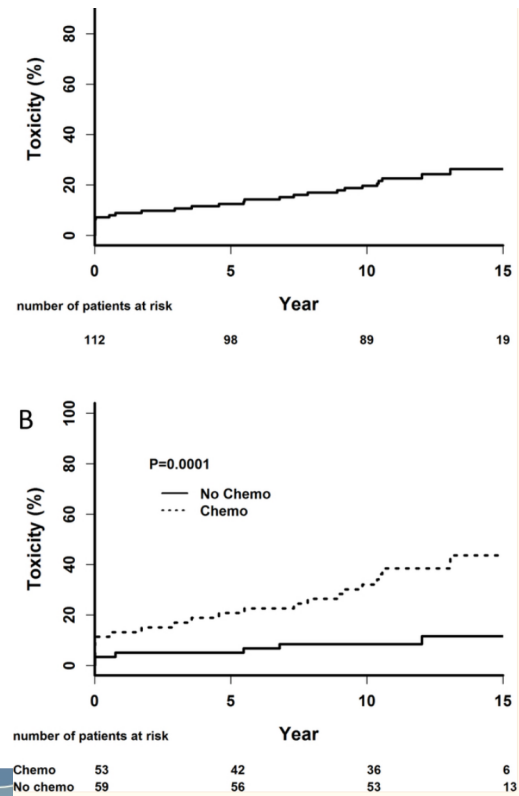
FIGURE 3

Overall clinical staging and adjuvant therapy. Number of patients (%). ECS, extracapsular spread. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Long-term Toxicities in 10-year Survivors of Radiation Treatment for Head and Neck Cancer

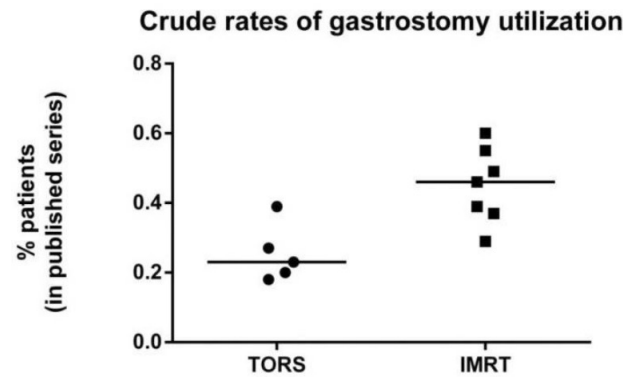
[Yanqun Dong](#), M.D., Ph.D.,¹ [John A. Ridge](#), M.D., Ph.D.,⁴ [Tianyu Li](#), M.S.,² [Miriam Lango](#), M.D.,⁴ [Thomas M. Churilla](#), M.D.,¹ [Jessica Bauman](#), M.D.,³ and [Thomas J. Galloway](#), M.D.¹

Kaplan–Meier curve of pharyngeal-laryngeal toxicity in all patients (A) and in patients treated with chemotherapy vs those without chemotherapy (B)



FUNCTIONAL OUTCOMES AFTER TORS FOR OROPHARYNGEAL CANCER: A SYSTEMATIC REVIEW

[Katherine A. Hutcheson](#), PhD, [F. Christopher Holsinger](#), MD, [Michael E. Kupferman](#), MD, and [Jan S. Lewin](#), PhD



	N	Crude PEG rate
TORS ± adjuvant therapy		
Hurtuk et al (2011) ¹²	54	20%
Genden et al (2011) ¹³	28	23%
Moore et al (2009) ¹¹	45	18%
Moore et al (2012) ¹⁶	66	27%
Leonhardt et al (2012) ¹⁹	38	39%
IMRT ± systemic therapy		
Bhayani et al (2013) ⁵	440	60%
May et al (2013) ²¹	170	55%
Hodge et al (2007) ²²	52	46%
Al-Mangani et al (2013) ²³	191	49%
Mendenhall et al (2010) ²⁰	130	39%
Sanguinetti et al (2012) ²⁴	59	37%
Feng et al (2010) ²⁵	73	29%



Some things I've learned about HPV+ OPSCC

- Not all early stage patients are good candidates for surgery...from a functional standpoint
- All early stage patients are good candidates for radiation....from a curative standpoint

- Surgery first(TORS/ND) can reduce the dose or extent of radiation to important structures related to eating, drinking, swallowing and dental function.....in selected patients

- Surgery first(TORS/ND) can result in the need for more radiation and/or chemotherapy than would have been used in the definitive setting....upstaging

Selecting the right patient for surgery in OPSCC Based Upon Exam(scope) and CT w/contrast

- Tumor Laterality -Unilateral
- Tumor Size -T1/T2
- Tumor Extent -Not to soft palate, midline or through constrictors
- Tumor Site -Tonsil better than BOT
- Nodal Stage/Site/Location/Number
 - N1, Level 2a, Not compressing IJV/SCM/Skin, One node
- Discussion with Med Onc/Rad Onc/Surgeon prior to scheduling

Objectives

- Discuss the current guideline-based management of HPV+ OPSCC
- Review common pre-treatment multidisciplinary considerations
- Prepare for evidence-based answers to frequent questions that patients ask when newly diagnosed
- Understand the approach to consideration of surgical treatment options
- **Analyze the role of liquid biopsy or ctDNA in OPSCC**
- Recognize why long-term surveillance and survivorship is different for OPSCC patients than other patients with lung or breast or prostate cancers

Table 2. Studies investigating ctHPV DNA as a cancer surveillance tool after definitive treatment.

Author/Trial Name	Number of Cases	Study Design	Detection Method	Definitive Treatment
Cao et al. [33]	14	SI, RA	qPCR	CRT
Routman et al. [43]	32	SI, RA	qPCR	Surgery
Ahn et al. [8]	93	SI, RA	qPCR	CRT/surgery
Berger et al. [44]	1076	MI, RA	ddPCR	CRT/surgery
Agrawal et al. [45]	135	SI, RA	qPCR	CRT/surgery
Veyer et al. [29]	66	SI, RA	ddPCR	CRT/surgery
Haring [46]	34	SI, PA	ddPCR	CRT/Surgery
Chera [47]	115	SI, PA	qPCR	CRT
Rutkowski [48]	66	SI, RA	qPCR	CRT

SI—single institutional study; MI—multi-institutional study; RA—retrospective analysis; PA—prospective analysis.

Adilbay D, et al. Circulating Human Papillomavirus in Head and Neck Squamous Cell Carcinoma: Possible Applications and Future Directions. *Cancer*. 2022;14:5946.



[Cancers \(Basel\)](#), 2022 Dec; 14(23): 5946.

Published online 2022 Dec 1. doi: [10.3390/cancers14235946](https://doi.org/10.3390/cancers14235946)

PMCID: PMC9740011

PMID: [36497430](https://pubmed.ncbi.nlm.nih.gov/36497430/)

Circulating Human Papillomavirus DNA in Head and Neck Squamous Cell Carcinoma: Possible Applications and Future Directions

[Dauren Adilbay](#),¹ [Saudamini Lele](#),¹ [John Pang](#),¹ [Ameya Asarkar](#),¹ [Jason Calligas](#),¹ and [Cherie-Ann Nathan](#)^{1,2,*}

- Circulating tumor HPV DNA (ctHPV DNA) is a potential biomarker for OPC attributed to HPV
- Investigated to select patients for de-escalation therapy
- May be used in surveillance and may have a comparable or higher specificity relative to current surveillance modalities



Association of Oral Human Papillomavirus DNA Persistence With Cancer Progression After Primary Treatment for Oral Cavity and Oropharyngeal Squamous Cell Carcinoma

Carole Fakhry, MD; Amanda L. Blackford, ScM; Geoff Neuner, MD; Weihong Xiao, MD; Bo Jiang, BS; Amit Agrawal, MD; Maura L. Gillison, MD, PhD

- Prospective case series of 396 patients with newly diagnosed oral cavity or oropharyngeal HNSCC
- Oral rinses were prospectively collected at diagnosis, weekly during radiation, and at completion of primary therapy
- HPV was detected using qPCR.

Fakhry C, et al. Association of Oral Human Papillomavirus DNA Persistence With Cancer Progression After Primary Treatment for Oral Cavity and Oropharyngeal Squamous Cell Carcinoma. *JAMA Oncology*. 2019; 5(7):985-992.

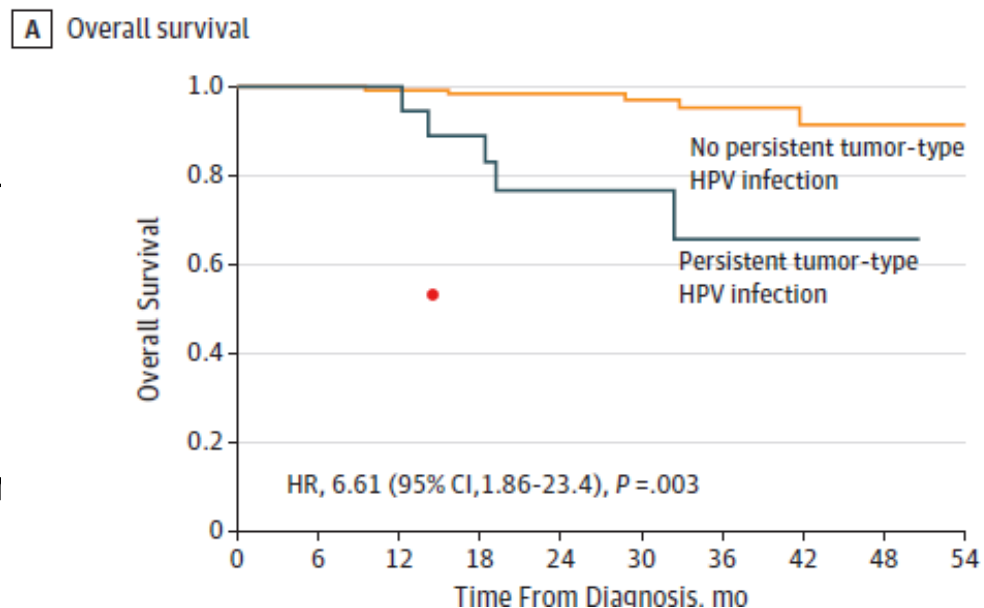
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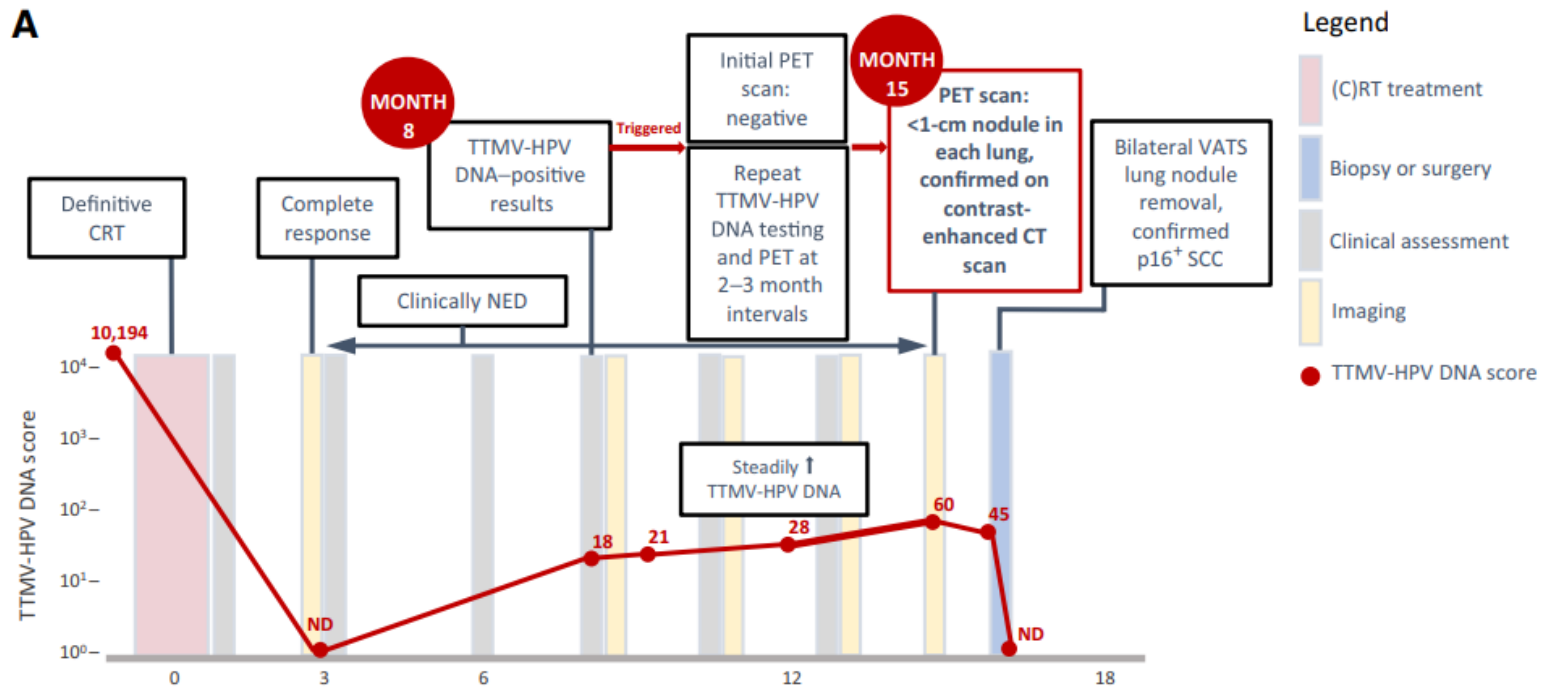
Results

- HPV identical in type between tumor and oral rinses at diagnosis was detectable in 80% of patients with HPV+ OPSCC
- Persistent detection of HPV DNA after completion of primary treatment was significantly associated with decreased OS



Fakhry C, et al. Association of Oral Human Papillomavirus DNA Persistence With Cancer Progression After Primary Treatment for Oral Cavity and Oropharyngeal Squamous Cell Carcinoma. *JAMA Oncology*. 2019; 5(7):985-992.

How should we manage a positive test?



Berger B, et al. Detection of Occult Recurrence Using Circulating Tumor Tissue Modified HPV DNA among Patients with Treated for HPV-Driven Oropharyngeal Carcinoma. Clin Cancer Research. 2022, 28(19) 4292-4301.

- 115 patients were enrolled with 1,006 blood samples
- Median follow up of 23 months
- 87 patients had undetectable ctHPV DNA at all post treatment timepoints and none developed recurrence (NPV: 100%)
- 28 patients developed one positive ctHPV DNA post treatment (PPV 54%)
 - Median time to abnormal signal 12.3 months
- 16 patients had two consecutive positive ctHPV DNA
 - 15 developed biopsy proven recurrence
 - PPV 94%
- Median lead time between ctHPV DNA positivity and biopsy proven recurrence 3.9 months

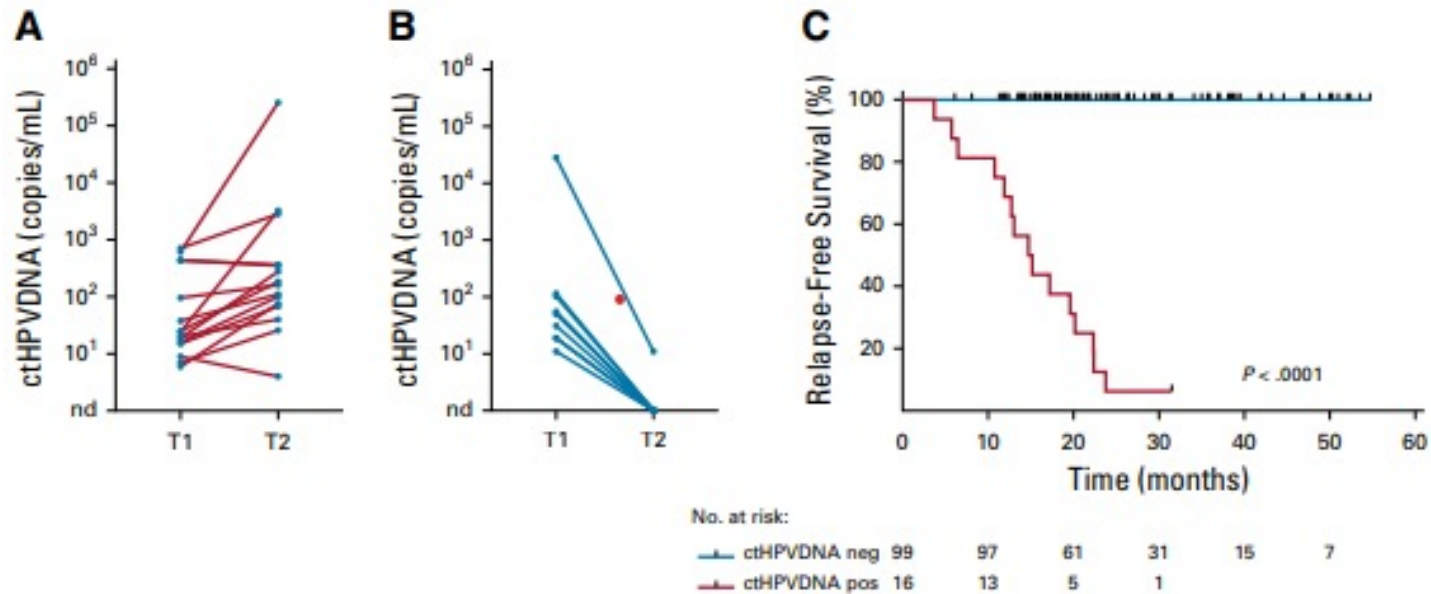
Chera B, et al. Plasma Circulating Tumor HPV DNA for the Surveillance of Cancer Recurrence in HPV-Associated Oropharyngeal Cancer. J Clin Oncology. 2020, 38:1050-1058.

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What happened to the patients who developed a positive ctHPV DNA post treatment?



Chera B, et al. Plasma Circulating Tumor HPV DNA for the Surveillance of Cancer Recurrence in HPV-Associated Oropharyngeal Cancer. J Clin Oncology. 2020, 38:1050-1058.

Association of Pretreatment Circulating Tumor Tissue-Modified Viral HPV DNA With Clinicopathologic Factors in HPV-Positive Oropharyngeal Cancer

Eleni M. Rettig, MD^{1,2,3,4}; Annette A. Wang, BS³; Ngoc-Anh Tran, MD^{3,5}; et al

> Author Affiliations

JAMA Otolaryngol Head Neck Surg. 2022;148(12):1120-1130. doi:10.1001/jamaoto.2022.3282

- Circulating TTMV HPV DNA was associated with nodal disease at HPV-positive OPSCC.
- A few patients with undetectable levels had predominantly clinical stage N0 disease, suggesting assay sensitivity for diagnostic purposes may be lower among patients without cervical lymphadenopathy.
- The use of this biomarker for surveillance of patients with undetectable baseline values, warrant further investigation.

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Detection of Occult Recurrence Using Circulating Tumor Tissue Modified Viral HPV DNA among Patients Treated for HPV-Driven Oropharyngeal Carcinoma

Barry M. Berger¹, Glenn J. Hanna², Marshall R. Posner^{3,4}, Eric M. Genden^{3,5}, Julio Lautersztain⁶, Stephen P. Naber¹, Catherine Del Vecchio Fitz¹, and Charlotte Kuperwasser¹



- Retrospective case series of 1,076 consecutive patients across 108 US sites
- Patients were ≥ 3 months post-treatment for HPV-driven OPSCC
- Had one or more TTMV-HPV DNA tests (NavDx, Naveris Laboratories) between Feb 2020 and June 2021.

Berger B, et al. Detection of Occult Recurrence Using Circulating Tumor Tissue Modified HPV DNA among Patients with Treated for HPV-Driven Oropharyngeal Carcinoma. Clin Cancer Research. 2022, 28(19) 4292-4301.

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- Circulating TTMV-HPV DNA was positive in 80 of 1,076 (7.4%) patients following definitive treatment
- At first positive test, 21 of 80 (26%) patients had known recurrence
- Of the remaining 59 patients, 55 (93%) subsequently had a confirmed recurrence
- Overall positive predictive value for recurrent disease is 95% (76/80)
- Overall negative predictive value for recurrent disease is 95% (1,198/1,256)

Berger B, et al. Detection of Occult Recurrence Using Circulating Tumor Tissue Modified HPV DNA among Patients with Treated for HPV-Driven Oropharyngeal Carcinoma. Clin Cancer Research. 2022, 28(19) 4292-4301.

- What is the benefit of early recurrence detection in HPV oropharyngeal cancers?
- Salvage treatment for HPV-negative oropharyngeal cancer
 - Surgery for locoregional recurrence: 2 yr OS ~50%
 - Re-irradiation for locoregional recurrence: 2 yr OS ~30%
- Salvage treatment for HPV+ OPSCC
 - Surgery for locoregional recurrence: 2 yr OS ~80%
 - Re-irradiation for locoregional recurrence: 2 yr OS ~70%

Zafereo M., et al. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. *Cancer*. 2009, Vol 115, Iss 24, 5723-5733.

Guo T., et al. Current perspectives on recurrent HPV-mediated oropharyngeal cancer. *Front. Oncol.* 2022;12:966899.

Objectives

- Discuss the current guideline-based management of HPV+ OPSCC
- Review common pre-treatment multidisciplinary considerations
- Prepare for evidence-based answers to frequent questions that patients ask when newly diagnosed
- Understand the approach to consideration of surgical treatment options
- Analyze the role of liquid biopsy or ctDNA in OPSCC
- **Recognize why long-term surveillance and survivorship is different for OPSCC patients than other patients with lung or breast or prostate cancers**

Surveillance and Survivorship



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2023 Head and Neck Cancers

[NCCN Guidelines Index](#)
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FOLLOW-UP RECOMMENDATIONS^a

(based on risk of relapse, second primaries, treatment sequelae, and toxicities)

- H&P exam (including a complete head and neck exam; and mirror and fiberoptic examination):^b
 - ▶ Year 1, every 1–3 mo
 - ▶ Year 2, every 2–6 mo
 - ▶ Years 3–5, every 4–8 mo
 - ▶ >5 years, every 12 mo
- AM cortisol, growth hormone (GH), free T4, prolactin, insulin-like growth factor 2 (IGF-2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), serum adrenocorticotropic hormone (ACTH), and total and bioavailable testosterone levels annually to evaluate panhypopituitarism following RT to the skull base.^c (category 2B)
- Imaging ([See Principles of Imaging, IMG-A](#))
- Thyroid-stimulating hormone (TSH) every 6–12 mo if neck irradiated.
- Dental evaluation^d for oral cavity and sites exposed to significant intraoral radiation treatment.
- Consider EBV DNA monitoring for nasopharyngeal cancer (category 2B).
- Supportive care and rehabilitation:
 - ▶ Speech/hearing and swallowing evaluation^e and rehabilitation as clinically indicated.
 - ▶ Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is stabilized.^e
 - ▶ Ongoing surveillance for depression ([See NCCN Guidelines for Distress Management](#)).
 - ▶ Smoking cessation^f and alcohol counseling as clinically indicated.
 - ▶ Lymphedema evaluation and rehabilitation, as clinically indicated. (See SLYMPH-A in the [NCCN Guidelines for Survivorship](#)).
- Integration of survivorship care and care plan within 1 year, complementary to ongoing involvement from a head and neck oncologist ([See NCCN Guidelines for Survivorship](#)).^g

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The importance of dental evaluation and hygiene

- Especially important before Radiation treatment
- **Xerostomia** has a detrimental effect on the teeth
 - Decay and osteoradionecrosis
- **Trismus** from invasion of the tumor to the masticator muscles or secondary to surgery or radiation
 - Minimized with physiotherapy and exercise
- NCCN has developed guidelines for dental evaluation
 - Pre, during, and post treatment
 - **Educating patients** - hydration, saliva substitutes, meticulous oral hygiene, dietary modifications (avoiding caffeine and alcohol) and frequent dental evaluations are the basis.

PRINCIPLES OF ORAL/DENTAL EVALUATION AND MANAGEMENT^{1,2}

RT to the head and neck causes xerostomia and salivary gland dysfunction, which dramatically increases the risk of dental caries and its sequelae, including dentoalveolar infection and osteoradionecrosis. RT also affects the dental hard tissues, which increases their susceptibility to demineralization³ within the presence of xerostomia, microbial changes following RT, and changes to a more cariogenic diet. IMRT and salivary gland-sparing techniques are associated with dose-dependent recovery of salivary function over time⁴ and with reduced risk for dental caries long term for some patients.⁵ Radiation-related caries and other dental hard tissue changes can appear within the first 3 months following RT.^{6,7}

Goals of Pre-RT Oral/Dental Evaluation:

1. Patient education, both oral and written, regarding oral and dental complications of RT and need for compliance with preventive protocols.

• Effect on salivary glands

- ▶ Dry mouth strategies
 - ◊ Increased hydration
 - ◊ Minimize ingestion of caffeinated products and alcohol
 - ◊ Salivary substitutes (eg, gels containing lysozyme, lactoferrin, peroxidase, and supersaturated calcium phosphate solutions)⁸
 - ◊ Alcohol-free mouthwash (stabilized 0.1% chlorine dioxide oral rinse preferred)
 - ◊ Salivary stimulation
 - Gustatory stimulants (eg, xylitol chewing gum, sorbitol/malic acid lozenges, xylitol lozenges)
 - Cholinergic agonists (eg, pilocarpine, cevimeline)^{9,10}

▶ Dental caries prevention

- ◊ Diet counseling
- ◊ Meticulous oral hygiene
 - Brushing teeth twice daily
 - Floss or interdental cleaner daily
 - Alcohol-free mouthwash twice daily

- ◊ High potency topical fluoride – continue long term after therapy
 - Daily 1.1% NaF gel or SNF₂ gel, brush on or in custom dental trays; or
 - Daily 1.1% NaF dentifrice; or
 - Fluoride varnish application, three times per year; or
 - Calcium phosphate artificial saliva rinse
- ◊ Regular frequent dental evaluations to detect dental disease
- ◊ Candidiasis prevention and control
 - Topical therapy (anti-fungal lozenges^a or suspensions)
 - Systemic antifungal therapy if refractory to topicals (consider infectious disease consult)

• Effect on bone in irradiated field

- ▶ Need for pre-RT dental evaluation and determine need for dental extractions^{5,11,12}
 - ◊ If yes, should be completed at least 2 weeks prior to start of RT
 - ◊ Long-term prognosis of teeth and patient motivation should be considered
 - ◊ Need to contact oncology team if any future extractions or surgery in irradiated field

• Effect on masticatory muscles – potential for trismus^{6,7}

- ▶ Maintain range of motion
 - ◊ Tongue blades and gentle stretching
 - ◊ Custom mouth-opening devices for rehabilitation of trismus and jaw motion

SPEECH AND SWALLOWING REHABILITATION

- Speech and swallowing function are commonly affected by the tumor and/or the related treatment
- Early involvement of a SLP is of the essence.
- Pre-treatment evaluation to establish the baseline of speech, voice, and swallowing.
- Pre-op counseling regarding expected post-treatment outcomes, rehabilitation and recovery expected.
- A visit once every 2 weeks during the RT treatment to optimize swallow function and maximize their post treatment outcomes.
- Nutrition assessment, NG or PEG tube if needed
- Speech/swallowing therapy continues until speech/swallow function is stable and optimized.

Conclusions

- Multidisciplinary Care for HPV+ OPSCC is essential
- Dental/Speech/Swallowing/Nutrition Prevention and Rehab is most important indicator of quality of life
- CT Scan with contrast necessary to determine if patient is candidate for curative surgery
- No guidelines supportive of liquid biopsy based surveillance to date