Clinical Uncertainties of Circulating Tumor DNA in Human Papillomavirus–Related Oropharyngeal Squamous Cell Carcinoma in the Absence of National Comprehensive Cancer Network Guidelines

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It is well-established that human papillomavirus (HPV) is etiologically responsible for a distinct subset of oropharyngeal squamous cell carcinomas (OPSCCs) and is an independent biomarker of improved prognosis. In light of this association, the National Comprehensive Cancer Network (NCCN) guidelines,[1] College of American Pathologists,[2] and ASCO[3] recommend assessment of HPV tumor status at diagnosis using either direct methods of HPV testing (eg, in situ hybridization or polymerase chain reaction) or a surrogate marker of HPV (ie, p16 immunohistochemistry) from primary tumor or nodal metastasis.

HPV-related 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%.[4-9] The majority of recurrences, approximately 66%-80%, occur within the first two years after treatment and are locoregional (54%).[10-13] Surgical salvage of recurrent disease is associated with better overall survival.[12] Furthermore, overall survival is significantly improved for patients with locoregional compared with distant recurrence.[11-13] Critical to optimal survival after recurrence is early identification when salvage is possible. Current NCCN guidelines for surveillance after treatment recommend history and clinical examination including mirror or fiberoptic examination every 1-3 months in the first year and every 3-6 months in the second year.[1] There are no imaging recommendations beyond obtaining post-treatment imaging only once to assess the response to radiation-based therapy or to establish baseline after primary surgical resection. The NCCN recommends against routine imaging surveillance; instead, the guidelines and data support obtaining imaging only for new symptoms or physical exam findings.[1]

The relationship between HPV and OPSCC is analogous to another virally mediated head and neck cancer—Epstein-Barr virus (EBV)–related nasopharyngeal cancer (NPC). In NPC, EBV is etiologically responsible for a subset of malignancies and is an independent biomarker of prognosis.[1,14] Determination of EBV tumor status at diagnosis is recommended by the NCCN.[1] For patients with EBV-related NPC and detectable circulating tumor DNA (ctEBV DNA) before treatment, ctEBV DNA is a dynamic biomarker of disease state and burden of disease.[14] Thus, ctEBV DNA levels are used to assess treatment response and are the basis for clinical treatment decision making. For example, the presence of ctEBV DNA post-treatment is associated with worse prognosis and is being evaluated as an indication for consolidation chemotherapy.[14,15]

Similar to EBV-related NPC, it appears that the detection of circulating tumor HPV DNA (ctHPV DNA) after treatment of HPV-related OPSCC is associated with worse prognosis and is predictive of clinical recurrence. Several observational cohort studies have shown that HPV DNA in oral rinse or plasma precedes clinical detection of disease recurrence (Table 1)[16-28]; however, this has not been investigated in clinical trials with uniform study design which limits translation to clinical practice. In the past year, a plasma ctHPV DNA assay has become commercially available (and others are in development), which advertises for determination of genotype at diagnosis, assessment of clinical response, and disease surveillance.[29] This assay uses droplet digital polymerase chain reaction (PCR) which, compared with conventional PCR, is able to identify DNA of interest with improved sensitivity, reproducibility, and precision.[30] The assay detects *E6* and *E7* genes encoded by HPV 16 and *E7* gene for HPV 18, 31, 33, and 35.[26]

While there is great enthusiasm that ctHPV DNA can be used in surveillance for earlier detection of recurrence in HPV-OPSCC, there are many unanswered questions within the head and neck cancer community. The literature that served as the basis for integration of

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TABLE 1. Summary of Published Studies Evaluating Human Papillomavirus DNA for Detecting Disease Recurrence or Persistence

Study	Design	Treatment Modality	Lead Time, Median (range)	Patients in Analysis, Total No.	Positive Test[a]	Primary Outcome Evaluated	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Chuang et al[17]	Prospective cohort	Not specified	3.5 months	20	Oral rinse	Recurrence	50.0	100.0	100.0	88.9
Ahn et al[18]	Retrospective cohort	Surgery and/or radiation	4.4 months	72	Oral rinse	Recurrence	25.0	98.3	75.0	86.8
				52	Plasma		62.5	97.7	83.3	93.5
				46	Oral rinse and plasma		66.7	95.0	66.7	95.0
Rettig et al[19]	Prospective cohort	Surgery and/or radiation	—	124	Oral rinse	Recurrence	35.7	99.1	83.3	92.4
Hanna et al[16]	Prospective cohort	Radiation, chemotherapy, or immunotherapy	19 days (13-38)	22	Increasing plasma ctHPV DNA levels	Progression of recurrent or metastatic disease	100.0	100.0	—	—
Fakhry et al[20]	Prospective cohort	Surgery and/or radiation	—	148	Oral rinse	Recurrence	33.3	90.1	42.9	85.8
Chera et al[26]	Prospective cohort	Radiation	3.9 months (0.37-12.9)	115	Two consecutive plasma tests	Recurrence	100.0	99.0	94.0	100.0
Reder et al[22]	Prospective cohort	Surgery and/or radiation	—	23	Plasma	Recurrence	100.0	83.3	62.5	100.0
Rutkowski et al[23]	Prospective cohort	Radiation	—	216	Plasma	Recurrence	100.0	98.0	83.0	100.0
Haring et al[27]	Prospective cohort	Chemotherapy and immunotherapy	—	12	≥ 60% increase in ctHPV DNA levels in plasma	Progression of recurrent disease	88.9	88.9	88.9	88.9
Tanaka et al[24]	Prospective cohort	Radiation	10 months	35	Plasma	Persistence or recurrence	66.7	100.0	100.0	89.7
Akashi et al[25]	Prospective cohort	Surgery and/or radiation	—	25	Plasma	Recurrence	100.0	100.0	—	—
Berger et al[28]	Retrospective case series	Not specified	—	1,076	Plasma	Recurrence	56.7	99.7	95.0	95.0

Abbreviations: ctHPV, circulating tumor human papillomavirus; NPV, negative predictive value; PPV, positive predictive value.
[a]Unless otherwise specified, a single positive test was considered positive.

ctEBV DNA in clinical decision making in both treatment and surveillance for EBV-related NPC may serve as a template for HPV-related OPSCC. In large population-based screening studies, detection of ctEBV DNA led to earlier diagnosis of NPC[31] as well as earlier detection of recurrence in the post-treatment setting.[14] After the positive ctEBV DNA test, magnetic resonance imaging was associated with increased odds of clinical findings relative to fiberoptic nasopharyngoscopy.[32,33]

In the published literature to date on HPV-related OPSCC, the lead time between positive plasma ctHPV DNA and clinical evidence of disease ranged from 19 days to 10 months, with the largest study identifying a median lead time of 3.9 months (range, 0.4-12.9 months).[26] Unfortunately, these analyses were not derived from prospective clinical studies with sample collection, clinical examination, and imaging at regular prescribed intervals, but rather from prospective studies with sampling at the time of clinical visits. In a retrospective case series analyzing 1,076 patients across the country, the time interval between the first two ctHPV DNA tests ranged between 9 and 367 days.[28] This introduces interval censoring, which suggests that the true lead time could not be observed as it lies between currently observed time points of clinical follow-up and imaging. Whether the exact lead time is shorter or longer than the current data suggest is unknown. To address this uncertainty and define a robust estimate of lead time, larger prospective studies comparing study participants with a designated schedule and order of sample collection, clinical examination, and imaging to participants undergoing NCCN recommended surveillance are needed.

Such rigorous studies are needed to inform whether the addition of ctHPV DNA to the present NCCN endorsed clinical surveillance alters the disease course in a clinically meaningful manner. Data are needed to determine whether differences in timing, type and extent of recurrence diagnosed, morbidity of salvage therapy, quality of life, and cost-effectiveness exist. If ctHPV DNA is observed to have clinical utility, such prospective studies will also inform frequency for ctHPV DNA use and its utility as an adjunct or alternative to clinical examination. A recent study suggests that testing for ctHPV DNA every 3 months is more cost-effective for post-treatment surveillance compared with currently used strategies, particularly for equivocal results that are resulting in repeated imaging studies.[34]

Critical to elucidating the reliability of an assay and its clinical role is understanding its performance characteristics and reproducibility. Generally, performance characteristics appear to vary based on the type of sample collection (oral *v* plasma), the DNA detection method (real-time PCR, droplet digital PCR, and NGS), and type of recurrence (local, regional, and/or distant). Pooled sensitivity for oral HPV DNA detection has been shown to be moderate (72%; 95% CI, 45 to 89) ranging from 25% to 100%, while specificity is higher with a pooled estimate of 92% (95% CI, 82 to 97) and a range of 88%-100%. The positive predictive value of oral HPV DNA to detect recurrence has ranged from 42.9% to 100% while the negative predictive value (NPV) has ranged from 85.8% to 100%.[35] Performance properties in plasma ctHPV DNA appear to be improved with ranges of sensitivity 63%-100%, specificity 83%-100%, positive predictive value 63%-100%, and NPV 89%-100% (Table 1). These studies consistently identify a high NPV. With a low complement to the NPV or false omission rate, it is expected that few patients with recurrent or persistent disease have undetectable ctHPV DNA. If the NPV of ctHPV DNA proves to be reliably high, it may be possible to investigate whether the frequency of clinical surveillance can be reduced for survivors with negative tests or if ctHPV DNA could supplant clinical examination. ctHPV DNA may also offer the opportunity to extend the window of surveillance beyond the currently accepted 3-5 years to identify and understand late recurrences. As with other surveillance tools, a positive ctHPV DNA test may assist with identifying patients who require further evaluation with diagnostic tests; however, prospective studies are needed to elucidate what the clinical and/or radiographic evaluation should entail after a positive ctHPV DNA test.

At present, ctHPV DNA detection without concurrent clinical or radiographic correlates represents an outcome without actionable implications outside of clinical trials. The magnitude of a positive ctHPV DNA test appears to be associated with disease burden[21,36]; however, there are no established cutoffs to guide a diagnostic evaluation to a locoregional or distant site, and the clinical significance of ctHPV DNA variation as a continuous variable is unknown. Moreover, the definition of an abnormal test has varied between studies—while one study defined two consecutive abnormal ctHPV DNA tests as criteria for positive,[26] others considered one abnormal test to be positive.[17-25] Notably, studies to date and commercially available assays have used heterogeneous HPV detection assays; validation is needed, especially of commercially available tests, as methods are expected to influence thresholds of positivity and performance characteristics. Establishing clear definitions of clinically meaningful positivity will be important for physicians and survivors.

Another important consideration in the absence of prospective data is the potential harmful psychological impact of ctHPV DNA on survivors between a positive test and clinical recurrence, and the impact of false positive tests and lead time bias. With better understanding of the kinetics, dynamics, and prognostic value of ctHPV DNA, we will be able to counsel patients on the meaning and significance of their test results when it is used as a method of surveillance.

Future studies should be designed with the goal of refining our understanding of lead time, clinical course following positive tests, and quality of life implications. In addition, robust prospective studies will allow us to also determine whether ctHPV DNA levels vary by race or gender. While HPV-OPSCC incidence is highest among White men, the prevalence of HPV-positive tumors is increasing significantly across all race and gender groups.[37-39] If ctHPV DNA

is included in clinical workflows, the acceptance of p16 as a surrogate for HPV status at diagnosis may need to be revisited, as determining the tumor type infection has been shown to be of relevance in the interpretation of ctHPV DNA levels.[19,20] Finally, the ctHPV DNA commercial assay presently only applies to plasma; however, published data support a role for evaluating HPV DNA in saliva,[21] oral rinses,[17-20,40] or pharyngeal brushings.[41] The performance characteristics for these, in addition to reproducibility and validation, will need to be determined, as the ease of saliva and oral rinse collection relative to venipuncture may be appealing to survivors and health care teams if the performance characteristics are similar.

In sum, while there is great enthusiasm for the emerging role of ctHPV DNA in the surveillance of HPV-OPSCC, it is incumbent upon us to recognize that physicians and survivors are in uncharted territory. There are significant knowledge gaps at this time, which introduce uncertainty as a commercially available assay is routinely used.

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