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A Hidden Epidemic of "Intermediate Risk" Oropharynx Cancer

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Objectives: Oropharyngeal squamous cell carcinoma (OPSCC) incidence is rapidly increasing in the United States and around the world, driven in large part by infection with the human papillomavirus (HPV). HPV associated OPSCC (HPV+OPSCC) has been shown to have improved response to treatment relative to tobacco-associated OPSCC. However, improvement in patient survival has not been uniform. Subsets of OPSCC patients in the US and around the world continue to have poor oncologic outcomes. Although the drivers of this phenomenon remain unclear, there is increasing evidence that tobacco exposure plays an important role in modulating HPV+OPSCC clinical outcomes.

Methods: We conducted a review of the literature.

Results: We discuss the potential biological and epidemiological interplay between tobacco and HPV exposure in the context of OPSCC. Multiple retrospective and prospective cohorts show that HPV+OPSCC patients with a history of tobacco exposure have response to treatment and clinical outcomes distinct from HPV+OPSCC non-smokers which poses clinical and scientific challenges to be addressed over the next decade.

Conclusions: The interaction between tobacco exposure and HPV infection in the context of OPSCC has significant implications for both standard of care treatment regimens and development of novel therapeutic approaches, in particular those which incorporate immunomodulatory agents.

Key Words: Oropharynx, HPV, tobacco, radiation, tumor immune microenvironment.

Level of Evidence: 5

RISING OROPHARYNGEAL SQUAMOUS CELL CARCINOMA INCIDENCE PRESENTS AN INCREASINGLY URGENT CLINICAL PROBLEM

Over the last two centuries, head and neck squamous cell carcinoma was a relatively rare entity, which was overwhelmingly attributable to tobacco and alcohol.[1] In the United States, these cancers primarily occurred in older male smokers.[1,2] Oropharyngeal squamous cell carcinoma (OPSCC), a subset of head and neck squamous cell carcinomas, has been rising sharply in incidence over the last two decades with no evidence that this trend will soon abate.[1,3] This rise in incidence now affects most age groups, including those over the age of 65, a cohort traditionally associated with tobacco related OPSCC development.[4] A recent analysis by Tota et al using registry data suggests a nearly 50% increase in the new cases of OPSCC diagnosed in the United States over the next two decades driven overwhelmingly by increased rates in elderly males.

Human papilloma virus (HPV) has long been known to be a major cause of cervical, penile, and anal cancer in the United States and the developing world.[5–7] It is now clear that HPV is also the primary driver of the increase in OPSCC diagnoses. Over the last two decades, preclinical and clinical studies have conclusively linked HPV to OPSCC tumorigenesis in a majority of new diagnoses in the United States.[8–12] Data from two Danish registry studies conducted over the first decade of this century demonstrate an incidence increase for HPV+OPSCC between 5% and 8% per year.[13,14] These data match that generated from a retrospective Dutch analysis which showed an increase in HPV positivity from 5% to nearly 30% over a two decade period.[15] Similar changes in incidence have been demonstrated in several Asian studies (Korea: 2.4%[16]; Taiwan: 6.9%[17]). Together, these data indicate that HPV+OPSCC is becoming an urgent global clinical problem.

As discussed below, the effect of HPV on OPSCC incidence has fundamentally transformed the way we think about screening and prevention, the way we consider treatment escalation and/or de-escalation, and the way we approach development of novel clinical trials.

NEW STAGING FOR HPV+OPSCC

In January of 2018, the 8th Edition of the AJCC Staging Manual was widely introduced into clinical

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practice in the United States. This change was prompted by a consistent finding of better survival for HPV+OPSCC as compared to HPV-negative OPSCC in phase II and III clinical trials as well as large retrospective series showing that incorporation of HPV status into the staging system dramatically improved the risk stratification of OPSCC patients.[1,8,18,19] Consequently, a new staging system was created exclusively for HPV+OPSCC, and as a result of this change most patients previously staged as III–IV are now staged as I–II, reflecting their high disease-free and overall survival (OS) at 2 years post-treatment.

This improvement in HPV+OPSCC survival is both dramatic and unexpected. In contrast to OPSCC, carcinomas at most other head and neck sites have demonstrated either stagnate or only modestly improving survival rates over the last two decades.[20,21] Despite significant advancements in radiation and surgical techniques and the introduction of targeted agents (ie, tyrosine kinase inhibitors, monoclonal antibodies) into clinical practice throughout the United States, HPV remains the primary driver of improved survival recorded among head and neck sites.[20–23] In contrast to oral cavity and laryngeal SCC, OPSCC survival has nearly doubled over the last two decades, almost certainly driven by the epidemiological shift from HPV negative disease to a preponderance of HPV positive OPSCC.[1,24,25]

Although the improvement in clinical outcomes portends well for individual patients and the OPSCC patient population as whole, there exists significant data which suggest that not all HPV+OPSCC diagnoses can be expected to have excellent outcomes, and that much work remains to be done to better understand what *drives* HPV +OPSCC treatment response and patient survival. In the following sections, we discuss the modifying effect of tobacco exposure on HPV+OPSCC clinical outcomes.

NEW OPSCC DIAGNOSES OCCUR IN THE CONTEXT OF A PERSISTENTLY HIGH RATE OF TOBACCO EXPOSURE

Concomitant with an explosion in the incidence of HPV-associated OPSCC (HPV+OPSCC), tobacco exposure, previously the primary carcinogenic driver of OPSCC has continually decreased in the US population.[26] There are, however, important caveats to this general observation.

Our current understanding of HPV effects on OPSCC tumorigenesis includes a significant temporal latency of several decades between initial HPV exposure and development of HPV+OPSCC.[27] As a result, for a majority of patients diagnosed today, initial HPV exposure is presumed to have occurred sometime between 20 and 30 years ago. For most individuals, smoking initiation occurs in the early teen years—20s; this is thus the primary formative time period for individual patients for deleterious behaviors such as continuation of tobacco exposure. Therefore, for patients with a new diagnosis of HPV+OPSCC, both HPV-associated risk and tobacco exposure will be defined not by current rates, but by the epidemiology of HPV and smoking of the 1980s–2000s. According to the Centers for Disease Control and Prevention (CDC) in 1990, 50% of US adults reported being ever smokers, with the highest rate occurring among individuals age 25–44 and those with fewer than 12 years of education; 23% of individuals consumed more than 25 cigarettes per day.[28] In 2000, the fraction of daily smokers remained at nearly 20%.[29] By 2011, daily smoking was reported by only 15% of US adults and heavy smoking (>30 cigarettes/d) had decreased to <10% of the population.[26]

Reductions in smoking have not occurred at an even pace across all populations. Tobacco exposure in the US population ranges from 15% (non-Hispanic whites) to 30% (Native American) of individuals[26] and remains high among Veterans (40%–100%), elderly individuals, and individuals with low socioeconomic status.[30,31] In the US socioeconomic status and race impact not only smoking rates but also the ability of patients to quit, with non-Hispanic blacks demonstrating the lowest rate and lowest interest in quitting which further decreased with advancing age. Recent increases in utilization of nontobacco-based nicotine delivery products by teenagers and young adults raise the potential for future increases in tobacco exposure over the coming decades if a significant fraction of users ultimately crossover to tobacco containing products.[32,33] Reductions in smoking rates across the rest of the world have been equally slow and somewhat uneven across geographic regions and demographic strata.[34–36]

Based on these data, a significant fraction of new patients with a diagnosis of HPV+OPSCC both in the United States and around the world is expected to have a history of significant tobacco exposure and this will likely disproportionately impact minority patients with low socioeconomic status.

TOBACCO AND HPV LIKELY GENERATE A COMPLEX BIOLOGICAL INTERACTION IN OPSCC

Diseases, which are primarily associated with tobacco exposure, can occur in nonsmokers. In these instances, existing clinical and preclinical data point to disease variants with distinct biology and oncologic outcomes. For instance, lung cancers in nonsmokers (~25%) demonstrate such distinct behavior that these cases are now considered as a separate clinical entity.[37–40] OPSCC presents an even more complicated biological and oncologic dilemma. HPV-associated OPSCC (HPV+OPSCC) is thought to be driven by inactivation of tumor suppressor pathways (ie, *TP53*, *Rb*) through direct and indirect interactions between viral proteins and host tumor cell proteins.[41] In the context of tobacco-associated squamous carcinomas in the head and neck region inactivating mutations in *TP53* and other tumor suppressors are the primary drivers of tumor biology.[42,43] The publicly available HPV+OPSCC genomic and epigenetic data sets remain significantly limited with respect to size making a direct comparison challenging. The most recent the cancer genome atlas (TCGA) analysis completed by our group suggests differential methylation based on HPV status, with enrichment of the *NANOG* and *MYC* pathways but most importantly differential infiltration by favorable immunocyte populations.[44] Unfortunately, this analysis was unable to more directly evaluate the interaction between tobacco and HPV status in a single disease site (OPSCC) due to limited sample size. The group

from Memorial Sloan Kettering Cancer Center has completed the most direct head to head analysis of HPV+ and HPV– OPSCC and identified several potentially actionable differential deletions along with a higher frequency of *TP53* mutations in HPV– OPSCC potentially related to tobacco exposure, yet a similar overall tumor mutation burden.[45] These data are suggestive but far from definitive with respect to a direct molecular tobacco—HPV interaction at the level of tumor cells.

Approximately one in three new OPSCC has complex etiologic exposure signatures, where HPV and tobacco exposure overlap and contribute to tumorigenesis and treatment response in a manner which remains poorly understood to date. Ang et al demonstrated in the last decade that patients with HPV+OPSCC and a history of tobacco exposure formed an intermediate-risk phenotype which manifested with worse survival compared to HPV +OPSCC in nonsmokers (<10 pack-years) and improved survival compared to HPV-OPSCC.[8] This finding has since been confirmed in multiple retrospective and prospective data sets.[46] It is important however to understand that the intermediate-risk phenotype is described by clinical behavior not by a well-understood biological mechanism. In large part, the difficulties associated with elucidating this interaction arise from two distinct but reinforcing problems. First, preclinical models which combine HPV and tobacco exposure are extremely limited and the basic science data are almost completely lacking. Second, clinical data sets provide very complex information which cannot easily help us focus our preclinical efforts as discussed in the following section.

TOBACCO UTILIZATION IS ASSOCIATED WITH DECREASED SURVIVAL IN HPV+OPSCC

Multiple clinical data sets indicate that tobacco exposure modulates clinical outcomes in HPV+OPSCC.[8] Most recently, Vawda et al found lower relapse-free survival and OS in current smokers versus never smokers or former smokers and a relative dose dependent decrease in OS as tobacco exposure increased (pack-year history). The relative effect size for OS exceeded 20%, a striking clinical effect size within the context of OPSCC equal to or greater than the impact of positive nodal status or extranodal extension and more than double the effect size of adding cisplatin to radiation-based treatment.[21,47–49] These data are consistent with a reanalysis of RTOG 0129 and RTOG 9003 data showing that risk of disease progression or death increased with increasing tobacco consumption as well as retrospective single institution series which demonstrated higher rates of recurrence and decreased survival among HPV+OPSCC patients with a history of tobacco exposure.[50,51] Precisely how this effect is generated however remains unclear.

HPV clearly contributes to the development of OPSCC in the presence or absence of tobacco exposure in a manner which provides epidemiological support for individual-to-individual transmission, through sexual encounters.[52] Conversely, HPV– OPSCC is associated with tobacco and alcohol exposure but not behavioral patterns related to sexual activity.[9] Whether alcohol or tobacco use increase risk of HPV+OPSCC remains debatable.[53] There are some data sets, which do suggest that HPV and tobacco exposure, may be synergistic in terms of increasing risk. In women, smoking history has been found to impact disease progression to HPV-mediated cancer.[54] Kreimer et al showed in a multinational cohort of healthy men a relatively low frequency of high-risk HPV strains which was relatively consistent across countries, but was increased 2.5-fold in the context of current tobacco use.[55] Anantharaman et al examined the interaction between HPV and smoking in head and neck cancer patients and control participants from multiple European centers and identified an additive effect on OPSCC development.[56] Smith et al concluded that tobacco and alcohol use impacted the relative risk of cancer development regardless of HPV serologic status.[57]

In addition to direct effects on OPSCC tumorigenesis, tobacco exposure is a critical driver of overall patient health. This includes a dramatic reduction in pulmonary health and an increased rate of chronic pulmonary disease[58,59] as well as an increased risk of cardiovascular disease and fatal cardiac events.[60–62] A large prospective study of British physicians identified a 2-fold increase in all-cause mortality associated with smoking, driven in large part by development of tobacco-associated malignancies and development of cardiopulmonary disease.[63] In the US population, smoking has been associated with a 3-fold higher rate of death and a reduction in life expectancy of over one decade.[64] Together, these data suggest that HPV+OPSCC smokers will have decreased long-term survival in part as a result of tobacco mediated effects on overall health and comorbidity burden. In addition, tobacco-associated comorbidities are also likely to impact short-term, disease specific survival through decreased treatment tolerance. Multiple studies have shown that patients with a higher comorbidity burden experience greater rates of treatment de-escalation and/or cessation/interruption resulting in reduced treatment efficacy and disease control.[65,66]

In summary, tobacco can interact directly with HPV as it relates to tumor biology in addition to modulating the overall health/all-cause mortality of any cohort of smokers with HPV+OPSCC. Since frail patients with a higher comorbidity burden will also generally demonstrate decreased treatment tolerance and more frequent treatment de-intensification, it is possible that the interaction between HPV and tobacco as it relates to clinical outcomes in OPSCC is in fact driven by at least three overlapping clinical/epidemiological phenomena which cannot be easily dissected using retrospective analysis of clinical data sets.

VARIABLE CLINICAL OUTCOMES FOR SUBSETS OF OPSCC PATIENTS

The staging change for HPV+OPSCC was foreshadowed by a comprehensive analysis from the University of Texas MD Anderson Cancer Center which demonstrated a clear progression in clinical outcomes as a function of disease characteristics. Specifically, younger patients, without a history of tobacco exposure and early T-classification tumors, demonstrated a

significant improvement in survival post-1995 compared to the previous half century. This transition was so dramatic that it erased the normal correlation between tumor, nodal and metastasis classification and survival, primarily due to the biological and treatment effects of HPV.[1] However, that same study as well as the Ang et al data set identified a subset of OPSCC patients with poor disease-free survival and OS, in line with historical data.[1,8]

More recently, analyses of subsets of US patients have indicated that the expected improvement in HPV +OPSCC survival is far from uniform. Several analyses of Veterans showed that a majority of patients maintained a high rate of heavy tobacco exposure.[2,67] Despite a positive impact of HPV positivity on disease-free survival and OS, survival rates for both HPV+ and HPV– disease were in line with the Ang et al intermediate-risk and high-risk rates and the low-risk group was essentially absent.[2,68] These characteristics were conserved in both White and African American patients, resulting in similar disease behavior and oncologic outcomes.[69] Data from RTOG 0129 and RTOG 0522 have been reanalyzed with a longer follow-up period and demonstrated that the OS and progression-free survival (PFS) rates for low-, intermediate-, and high-risk OPSCC patients persistent with a difference in PFS between low- and intermediate-risk groups of over 15%.[70]

Together these data provide a sobering reminder that not all new HPV+OPSCC patients should be expected to demonstrate uniform clinical outcomes and excellent survival. This is critically important in light of recent attempts to tailor treatment regimens to OPSCC to maximize survival and reduce treatment related toxicity.

TREATMENT ALGORITHMS AND CHANGING PARADIGMS

Treatment paradigms of the 1990s and 2000s were focused on maintaining therapeutic equipoise and escalation. These efforts are perhaps best exemplified by the PARADIGM and DeCIDE clinical trials which tested the addition of induction chemotherapy to concurrent chemoradiation to improve survival rates.[71,72] Neither study demonstrated an improvement in survival through the addition of induction chemotherapy although survival rates for both the standard of care and experimental arms were substantially higher than would have been expected from previous data sets and accrual was incomplete. Although failure to complete accrual was partially blamed for the failure of these studies, it is quite possible that these studies failed to detect an improvement in survival because outcomes were already improving in patients with advanced-stage OPSCC.

Current therapeutic paradigms have shifted in light of improved survival data for HPV+OPSCC. Given the excellent survival of most HPV+OPSCC patients, there is now an appropriate focus on de-escalation of treatment intensity to ameliorate treatment-related toxicity. This is particularly important as the demographics of HPV+OPSCC shift to an older patient cohort with more expected comorbidities and potentially lower tolerance for intense treatment regimens.[73] The first large randomized study to tackle the approach of de-escalation, RTOG 1016 tested whether cetuximab would be able to deliver noninferior OS and PFS compared to a cisplatin-based regimen. The trial focused exclusively on patients with HPV+OPSCC generating a homogeneity of patient cohort not present in any previous prospective clinical trial of this size. Despite utilization of an accelerated fractionation regimen, both OS and PFS were significantly inferior in the cetuximab arm of the trial compared to the cisplatin arm with a difference of over 10% in PFS at 5 years.[24] By extrapolation, it is possible that in a patient cohort enriched for intermediate-risk OPSCC, the inferiority of cetuximab could potentially have been even more dramatic.

Multiple other studies have been initiated in the last decade with a focus on de-escalation using a variety of approaches, including incorporation of surgery, de-escalation of radiation dose, and changes in chemotherapy strategies. The advent of immunotherapy and its introduction into the clinical armamentarium of oncologists treating OPSCC has added yet another dimension to these ongoing efforts at precision oncology for HPV+OPSCC. CheckMate 141 generated promising results, with nivolumab demonstrating a significant increase in OS compared to non-immunomodulatory systemic therapy and importantly a more favorable toxicity profile. These effects were measured in both p16+ and p16– tumors although the benefit appeared more pronounced in p16+ tumors.[74,75] It is expected that introduction of immunomodulatory agents earlier in the treatment course could generate even more favorable effects, although this remains to be demonstrated. Similarly, whether immunomodulatory agents can improve oncologic outcomes while decreasing overall treatment-related toxicity in low- and intermediate-risk OPSCC remains an open question.

As pointed out by multiple investigators, however, it is critical that current trials aimed at de-escalation regardless of approach (ie, targeted agents, immunotherapy) consider very carefully criteria for inclusion of patients.[70] In our opinion, despite difficulties associated with accurately ascertaining and quantifying tobacco exposure, significant efforts should be dedicated to the addition of tobacco exposure into inclusion criteria for de-intensification trials. As discussed below, this consideration is potentially even more important when considering incorporation of targeted agents and immunomodulatory agents into novel treatment regimens.

VARIABLE RESPONSE RATES SUGGEST DIFFERENTIAL BIOLOGY WITHIN THE SPECTRUM OF HPV+OPSCC

Despite the clear separation with regard to treatment response and survival generated by HPV status, there is increasingly clear evidence that HPV+OPSCC tumors do not behave in a homogeneous manner. HPV+OPSCC demonstrates unique clinical behaviors such as distant metastases to bone and solid organs other than lung.[11] This pattern of metastasis occurs over a delayed time frame and has the potential to radically change the manner in which surveillance for recurrence/distant metastasis is performed in this patient population.[76] Specifically, distant metastases to solid organs including brain will

require some modification of normal clinical surveillance questioning related to patient symptoms and also likely increase the relative utility of whole body positron emission tomography and dedicated brain imaging over the next 1–2 decades.[77–79]

Within the spectrum of HPV+OPSCC, gene expression profiles partially related to tumor metabolism have been recently shown to predict stratification of clinical outcomes and may serve as a future biomarker for treatment selection.[10] Precisely what drives stratification of biological behavior and treatment response in HPV+OPSCC remains unclear. However, we believe that data from other tumors strongly support a role for tobacco exposure. Castelletti et al showed distinct molecular models for lung cancer patients with a history of radiation exposure compared to patients with a history of tobacco exposure.[80] More specifically, tobacco exposure has been shown to impact patterns of KRAS mutations in lung cancers.[81,82] In addition, smoking has been shown to have a significant impact on genome wide methylation which can persist even following cessation of smoking.[83] Although mutations and methylation are likely to demonstrate long-term persistence, smoking-related changes in gene expression do appear to reverse following cessation, although the relative timing remains both unclear and highly variable.[84] Interestingly, the recent analysis by Harbison et al of HPV+OPSCC tumor with documented recurrence identified a mutational landscape similar to HPV-unrelated HNSCC tumors and metachronous recurrent OPSCC demonstrated a profile very similar to traditional, tobacco related tumors, including *TP53*, *CASP8*, and *FAT1* mutational events.[85] Although too small to address the question of tobacco exposure as a driver of the intermediate-risk phenotype and potentially genotype, this study does support the hypothesized biological interaction between conventional carcinogen exposure and HPV in the context of OPSCC.

In addition to driving tumor (parasite) biology, tobacco exposure also exhibits significant effects on host biology through alterations of antitumor and systemic immunity and inflammation.[86] Tobacco effects on circulating immunocytes have been well established in the literature and have been shown to be both profound and relatively cell type specific.[87–89] Most recently, analysis of TCGA data for both head and neck squamous cell carcinoma and lung squamous cell carcinoma demonstrated a smoking signature that includes a higher mutational load and variable effects on tumor immunity. Critically, smoking generated opposing effects in head and neck squamous cell carcinoma and lung squamous cell carcinoma as it relates to tumor immunity, highlighting our difficulties in generating rational immunomodulatory approaches for HPV+OPSCC.[90] This difficulty is further augmented by the clear interaction between tumor characteristics (ie, mutational burden/profile) and the tumor immune microenvironment, generating differential responses to immunomodulatory agents as has been demonstrated in lung cancer patients.[91]

CONCLUSIONS

HPV+OPSCC is an increasingly prevalent clinical problem in the United States and around the world. Fortunately, many HPV+OPSCC patients have an excellent response to treatment, resulting in concomitant excellent survival. This has prompted significant changes in staging, and increased interest in de-escalation of treatment intensity. However, it is now clear that within the spectrum of HPV+OPSCC disease, there are patient subsets which continue to experience poor treatment response and survivorship. These patients have a disproportionate exposure to tobacco, which may explain their different survival characteristics. Although the interaction between HPV and tobacco in the context of OPSCC remains poorly understood and is likely multifactorial, its effects on clinical outcomes are important and cannot be ignored. Focused investigation is needed to elucidate this critical intersection of biology and epidemiology to better understand the behavior and optimize the treatment of intermediate-risk OPSCC.

It is important to note that even current efforts aimed directly at improving outcomes for intermediate-risk HPV+OPSCC such as EA3161 (phase II/III Randomized Study of Maintenance Nivolumab vs. Observation in Patients with Locally Advanced, Intermediate Risk HPV-Positive Oropharyngeal Cancer) are essentially based solely on a risk-stratification schema defined by reported tobacco exposure as opposed to clear biological framework for this disease. In some ways, this parallels the experience with de-escalation regimens targeting HPV+OPSCC more broadly since the mechanisms which might drive increased chemo- and radio-sensitivity in HPV driven tumors continue to remain unclear. In our opinion, there is a critical need for well-defined translational efforts in this area using preclinical models of HPV+OPSCC and preclinical models of acute and chronic tobacco exposure which can allow us to study both intrinsic tumor biology and the tumor immune microenvironment associated with HPV+OPSCC. Without such preclinical models, mechanistic studies will continue to lag clinical data, and we risk failure of multiple current and planned therapeutic clinical trials.

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