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ORIGINAL-RESEARCH-ARTICLE

Impact of Human Papillomavirus Status on Hypercoagulable Events in Oropharyngeal Squamous Cell Carcinoma

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Abstract

Objective: To determine whether HPV status impacts the incidence of hypercoagulable events in patients with OSCC.

Methods: Medical records for n=143 patients with a clinical diagnosis of OSCC and documented HPV status were abstracted from a head and neck cancer data base at Cooper University Hospital in Camden, NJ. Data regarding demographics, malignancy staging and treatment, clinical variables, and hypercoagulable events were recorded from the database and electronic medical record. Primary outcomes included the occurrence of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, and/or transient ischemic attack (TIA) either before, during, or after treatment of OSCC. Logistic regression modeling and fisher exact testing were utilized to compare rates of hypercoagulable events in HPV positive and HPV negative OSCC patients.

Results: Logistic regression modeling revealed odds ratios (OR) with no statistically significant relationship between HPV positive status and rates of DVT [OR: 0.9804, 95% CI (0.225, 4.278)], PE [OR: 0.584, 95% CI (0.36, 9.40)], stroke [OR: 0.363, 95% CI (0.123, 1.020)], and TIA [OR: 0.278, 95% CI (0.049, 1.575)]. Fisher exact testing revealed similar results for DVT (P=1.0), PE (P=1.0), stroke (P=0.062), and TIA (P=0.195).

Conclusion: Overall, no significant differences were identified in the rates of hypercoagulable events in HPV positive compared to HPV negative cohorts, suggesting the virus has no impact on thrombosis risk in OSCC patients.

1 | INTRODUCTION

Human Papillomavirus (HPV) is a prevalent cause of oropharyngeal squamous cell carcinoma (OPSCC). Though classically associated with major risk factors such as tobacco and alcohol use, OPSCC has been increasingly associated with HPV infection. A recent meta-analysis showed the prevalence of HPV related OPSCC has exponentially increased over time with the virus impacting 40.5% of cases before 2000, 64.3% between 2000-2004, and 72.2% between 2005-2009.(1) As the burden of HPV related OPSCC

expands, physicians are not only challenged to manage nuances in clinical treatment, but also mitigate secondary morbidity and mortality related to coagulopathic adverse events in this new, emerging population.

At the molecular level, OPSCC exhibits high thrombo -sis risk due to its association with increased expression of procoagulant proteins, microparticles, and cytokines.(2),(3), (4),(5),(6) It has been suggested that such molecular alterations may be responsible for increased incidence of local thrombotic events in OPSCC patients, such as internal jugular vein and carotid thrombosis.(7), (8),(9) Despite OPSCC's increased risk of thrombosis at the molecular and local level, a recent study using animal models with OPSCC demonstrated no elevated systemic thrombosis risk due to storage pool deficiency in platelets.(2) Such paradoxical thrombotic behavior of OPSCC has challenged physicians to properly assess venous thromboembolism (VTE) risk in OPSCC patients.

Notably, there remains a lack of high quality research related to VTE incidence and prophylaxis in head and neck cancer patients. While retrospective reviews have estimated the risk of VTE for general otolaryngology patients to be 0.1%- 2.4%, the risk of VTE has been reported to increase to 1.4% - 5.8% following surgical resection and microvascular reconstruction. It is understood that the presence of cancer as well as surgical operation increase the risk of VTE by 6.5 and 20 fold respectively. 19 However, as OPSCC is uniquely associated with HPV related pathogenesis and minimally invasive surgical techniques such as transoral robotic surgery, it has yet to be considered how the risk of VTE may differ in this emerging head and neck cancer population. As the second leading cause of mortality in cancer patients, VTE can pose a significant threat to head and neck cancer patients' overall survival. (10) There fore, better indicators of VTE risk in the OPSCC population are necessary to deliver appropriate levels of VTE prophylaxis.

As HPV is now implicated in over 70-80% of all OPSCC cases in North America and Europe, the impact of the virus on the incidence of hypercoagula- ble events in OPSCC patients has yet to be considered. (11) This retrospective cohort study explores whether HPV status correlates with the rate of overall incidence of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, and transient ischemic attack (TIA) before, during, or after OPSCC diagnosis and treatment.

2 | METHODS

This retrospective study was conducted at Cooper University Hospital in Camden, NJ and obtained approval from its associated Institutional Review Board (IRB number: 20-014). All individuals with a clinical diagnosis of OPSCC and documented HPV status were identified using an institutional database that recorded all cases of head and neck cancer between January 2005 and December 2018. Data regarding demographics, malignancy staging and treatment, clinical variables, and hypercoagulable events were recorded from the database and electronic medical record. Clinical staging of malignancy was conducted according to the 8th edition American Joint Committee on Cancer guidelines.(12) For deceased individuals, age was calculated as age at time of death. Hypercoagulability was assessed through the occurrence of DVT, PE, stroke, and/or TIA before, during, or after treatment of OPSCC. Logistic regression modeling and fisher exact testing were utilized to compare rates of hypercoagulable events in HPV positive and HPV negative patients.

3 | RESULTS

A total of 218 individuals with a clinical diagnosis of OPSCC were identified using the institutional head and neck cancer database. Of the 218 individuals, 75 were excluded due to a lack of recorded HPV status. A final cohort of 143 patients included n=53 HPV negative and n=90 HPV positive individuals.

Baseline clinical, demographic, and substance use characteristics are shown in table 1. In both cohorts, the mean age was approximately 64 years, and greater than 50% were Caucasian males. Systemic comorbidities were common with more than half of each cohort reporting hypertension and more than a quarter of each cohort reporting hyperlipidemia. The

Supplementary information The online version of this article (https://doi.org/10.52845/JORR/2023/4.3.5) contains supplementary material, which is available to authorized users.

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The distribution of associated tumor clinical staging and treatment modalities is shown in table 2. The overall clinical staging was similar between cohorts with approximately 62-64% of individuals with stage 4 malignancies. Tumor resection and chemotherapy rates were also quite similar between cohorts. Higher rates of immunotherapy and radiation treatment were recorded in the HPV positive cohort. In the HPV negative cohort, data related to radiation dosing was available for n=25 individuals and duration for n=28 individuals. In the HPV positive cohort, data related to radiation dosing was available for n=60 individuals and duration for n=61 individuals.

Table 1- *Demographic, Substance Use, and Clinical Characteristics*

	HPV Negative (n=53)	HPV Positive (n=90)
Age*	64.6 +/- 10.5	64.5 +/- 10.1
Male Sex**	36 (68%)	72 (80%)
Race**	36 (68%) White 13 (25%) Black 2 (4%) Asian 2 (4%) Other	71 (79%) White 14(16%) Black 3 (3%) Asian 2 (2%) Other
Tobacco Use**	5 (9%) Never Use 30 (57%) Current Use 17 (32%) Former Use 1 (2%) Unknown	32 (36%) Never Use 26 (29%) Current Use 32 (36%) Former Use 0 (0%) Unknown
Alcohol Use**	20 (38%) Never Use 29 (55%) Current or Former Use 4 (8%) Unknown	35 (39%) Never Use 53 (59%) Current or Former Use 2 (2%) Unknown
HTN**	28 (53%)	53 (59%)
T2DM**	12 (25%)	16 (18%)
HLD**	19 (36%)	41 (46%)
Coagulopathy**	0 (0%)	4 (4%)
Chronic Anticoagulation Therapy**	9 (17%)	8 (9%)
*mean +/- standard deviation **N (%) HTN Hypertension, T2DM Type 2 Diabetes Mellitus, HLD Hyperlipidemia		

Overall, 8 reports of DVT (n=5 HPV negative, n=3 HPV positive), 2 reports of PE (n=1 HPV negative, n=1 HPV positive), 17 reports of stroke (n=10 HPV negative, n=7 HPV positive), and 6 reports of TIA (n=4 HPV negative, n=2 HPV positive) were recorded. Logistic regression modeling revealed overall decreased odds ratios with no statistically significant relationship between HPV positive status and rates of DVT [OR: 0.9804, 95% CI (0.225, 4.278)], PE [OR: 0.584, 95% CI (0.36, 9.40)], stroke [OR: 0.363, 95% CI (0.123, 1.020)], and TIA [OR: 0.278, 95% CI (0.049, 1.575)]. Fisher exact testing revealed similar statistically insignificant results for DVT (P=1.0), PE (P=1.0), stroke (P=0.062), and TIA (P=0.195).

Table 2- *Tumor Staging and Treatment Modalities*

	HPV Negative (n=53)	HPV Positive (n=90)
Clinical Stage**	0: 2 (4%) 1: 2 (4%) 2: 5 (9%) 3: 3 (6%) 4: 34 (64%) Unknown: 7 (13%)	0: 0 (0%) 1: 6 (7%) 2: 6 (7%) 3: 10 (11%) 4: 56 (62%) Unknown: 12 (13%)
Tumor Resection**	17 (32%)	27 (30%)
Chemotherapy**	27 (51%)	46 (51%)
Immunotherapy**	2 (4%)	11 (12%)
Radiation**	30 (57%)	64 (71%)
Radiation Dose (cGY)*	6359.9 +/- 6685	6464.3 +/- 2551
Radiation Duration (days)*	47.1 +/- 17.7	47.5 +/- 14.1
*mean +/- standard deviation **N (%)		

4 | DISCUSSION

To our knowledge, the relationship between HPV status and rates of adverse hypercoagulable events in the clinical setting has yet to be examined, and thus, the overall objective of this study was to explore if such a relationship existed. From this retrospective cohort study, we were able to conclude that no statistically significant relationship exists between HPV status and rates of DVT, PE, stroke, and TIA in OPSCC patients.

Accurate estimation of the risk of adverse hypercoagulable events in OPSCC patients remains important as clinicians are tasked with balancing the risk of VTE and the risk of bleeding when delivering thrombosis prophylaxis.(13) currently, the reported risk of VTE in head and neck cancer has varied in the literature. A recent meta-analysis that assessed the incidence of thromboembolism in patients diagnosed with cancer according to its localization found the overall incidence of VTE in head and neck cancer patients to range from 0.16% to 3.125%. (10) Despite determining that head and neck cancer had one of the lowest VTE risks by site,

the meta-analysis included one study which determined head and neck cancer to have the second highest VTE risk by site, following only pancreatic cancer.14 Such discrepancies have challenged estimations of true VTE risk in head and neck cancer patients. However, determining that HPV status has no statistically significant correlation with rate of DVT, PE, stroke, and TIA, our study supports the assumption that HPV does not have an impact on VTE risk in OPSCC patients, and that bias inherent to prior individual studies may best explain the discrepancies of reported outcomes.10 Physicians should continue to consider established guidelines and risk stratifications for VTE risk management in OPSCC patients.(15), (16), (17)

Notable limitations of our study include our limited sample size of n=143 patients which may have limited our study's power to detect a significant difference at the p=0.05 level. Additionally, as our study only assessed the association between HPV status and hypercoagulable events, it was unable to determine causality and further consider provocative factors such as possible recent surgery and/or immobilization that might have served as confounding variables.(18) Finally, the utilization of an electronic medical record and head and neck cancer database from a singular institution may have limited data availability as outcomes of interest may have been recorded at outside institutions, thus limiting our study's ability to detect all experienced hypercoagulable events.

In conclusion, our study found no statistically significant relationship between HPV status of OPSCC and rate of adverse hypercoagulable events. (19) Our results indicate that HPV status should not play a significant role in the estimation of coagulopathy risk in OPSCC patients and suggest physicians should consider additional clinical factors when determining thrombosis risk and prophylaxis in OPSCC patients.

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