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PREVALENCE OF HPV BIOMARKERS IN ORAL RINSES AND SEROLOGY FOR HPV-RELATED OROPHARYNGEAL CANCER

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Abstract:
Background and objectives: *Infection with human papillomavirus (HPV) is the primary cause of oropharyngeal squamous cell cancer (OPC) in the United States. The main objective of the study is to analyse the prevalence of HPV biomarkers in oral rinses and serology for HPV-related oropharyngeal cancer.* ***Material and methods:*** *This descriptive study was conducted in SIMS, Lahore during June 2019 to January 2020. Participants also had blood collected post-therapy, when possible, at follow-up visits targeted during routine clinical follow-up around 9, 12, 18 and 24 months after diagnosis. A detailed computer assisted self -interview (CASI) risk factor survey, tumor sample, and oral rinse and gargle sample, were also collected around diagnosis.* ***Results:*** *Most (85%; 98/115) HPV-OPC cases were HPV16 E6 seropositive at diagnosis. Median age of patients was 56 years, 90% were male, 56% were never smokers, and 95% were American Joint Committee on Cancer (AJCC) stage III or IV. Comparing HPV-OPC cases that were seropositive versus seronegative for HPV16 E6 antibodies at diagnosis, characteristics were similar for stage, oropharyngeal subsite, age, gender, and risk behaviors, but HPV16 E6 seropositive cases were more likely to be Caucasian and to have a higher HPV16 DNA copy number detected in oral exfoliated cells.* ***Conclusion:*** *It is concluded that HPV-OPC post-treatment includes a variety of frequent clinical and radiological examinations that are based on standard oncological surveillance protocols rather than being specific for HPV related disease, and does not currently include serologic or virologic testing.*

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INTRODUCTION:

Infection with human papillomavirus (HPV) is the primary cause of oropharyngeal squamous cell cancer (OPC) in the United States. Following treatment, HPV-driven oropharyngeal cancer (HPV-OPC) has good survival, with a 5-year survival rate of 82%. While recurrence risk remains low among HPV-OPC, current standard of care surveillance includes intensive post therapy monitoring that could include physical exam, fiberoptic examinations, and radiologic imaging procedures [1]. These procedures are associated with significant time, resources, and additional costs. Post-treatment biomarkers are needed to risk stratify which patients are candidates for reduced surveillance intensity and which patients remain at higher recurrence risk [2].

Recent research demonstrates that HPV16 serum antibodies are present for many years before diagnosis of HPV-OPC, likely the result of unidentified oropharyngeal precursor lesions. We expect these pre- premalignant or early cancers arise from long-term oropharyngeal HPV16 infection, although this natural history has not yet been fully elucidated [3]. In contrast, HPV16 antibodies are rare in healthy controls (<1%). At the time of diagnosis, HPV16 E6 antibodies are detected in most HPV-OPC cases. Importantly, HPV16 E6 serology is not a good marker for predicting risk of cervical cancer (another HPV-related cancer), increasing its potential for predicting HPV-OPC specifically when detected [4].

Since the International Agency for Research on Cancer (IARC) classified Human papillomavirus (HPV) 16 as 'oncogenic' to a number of cancer sites [1] our understanding of the molecular, clinical and epidemiological aspects of oropharyngeal squamous cell carcinoma (OPSCC) has dramatically improved. At the same time, the global burden of the disease has steadily increased and it has been predicted to surpass cervical cancer in some developed countries [5]. An examination of accumulated knowledge regarding the HPV-related OPSCC disease thus far is warranted.

The main objective of the study is to analyse the prevalence of HPV biomarkers in oral rinses and serology for HPV-related oropharyngeal cancer.

MATERIAL AND METHODS:

This descriptive study was conducted in SIMS, Lahore during June 2019 to January 2020. Participants also had blood collected post-therapy, when possible, at follow-up visits targeted during routine clinical follow-up around 9, 12, 18 and 24 months after diagnosis. A detailed computer assisted self -interview (CASI) risk factor survey, tumor sample, and oral rinse and gargle sample, were also collected around diagnosis. Medical record abstraction was performed every six months for recurrence and survival. Of 166 HPV-OPC patients enrolled, 115 (69%) had a blood sample collected at diagnosis, and 64 (39%) had at least one post-treatment blood sample collected. Analysis for this project was restricted to subjects with blood samples, with trajectories in antibody levels explored among the 64 subjects with 2 or more blood samples collected.

The data was collected and analysed using SPSS version 17. All the values were expressed in mean and standard deviation.

RESULTS:

Most (85%; 98/115) HPV-OPC cases were HPV16 E6 seropositive at diagnosis. Median age of patients was 56 years, 90% were male, 56% were never smokers, and 95% were American Joint Committee on Cancer (AJCC) stage III or IV. Comparing HPV-OPC cases that were seropositive versus seronegative for HPV16 E6 antibodies at diagnosis, characteristics were similar for stage, oropharyngeal subsite, age, gender, and risk behaviors, but HPV16 E6 seropositive cases were more likely to be Caucasian and to have a higher HPV16 DNA copy number detected in oral exfoliated cells.

Table 01: Risk of recurrence among HPV-OPC cases, by level of HPV16 E6 antibody level at diagnosis.

HPV16 E6	**HR (95% CI)**
Per log increase	1.81 (0.47, 6.92)
Per 1000 MFI increase	1.13 (0.91, 1.40)
By tertile of MFI[a]	
Lowest	1.00
Middle	0.67 (0.11, 4.00)
Highest	1.90 (0.45, 7.96)

DISCUSSION:

Since the incidence of HPV-related OPSCCs is rapidly increasing, there is an urgent need to implement the most clinically valid HPV diagnostic assays to correctly classify true HPV-driven OPSCC and to rule out cancers with transient or oncogenic irrelevant HPV [6]. This is important, in an era in which de-escalation treatments are available and can avoid late toxicity in those young patients with potential better prognosis. It is also necessary to emphasise that the best strategy to fight against cancer is prevention, especially when the pathogenic agent is known and identifiable and the primary prevention tool such as HPV immunisation is available [7].

HPV16 E6 seroprevalence had the highest sensitivity (i.e. least false negatives) for HPV-OPC disease of the markers considered. E7 seroprevalence was lower among cases, consistent with previous research which showed E7 also has poorer specificity (i.e. has false positives) [8]. While most (85%) of HPV-OPC were HPV16 E6 seroprositive, the combined marker of any E1, E2 or E6 seroprevalence identified an additional 10% of cases, for a total sensitivity of 95% of HPV-OPC cases. One type, HPV31, had low E6 but high E7 seroprevalence, which may be due to HPV31 E6 protein sequence variation [9,10].

CONCLUSION:

It is concluded that HPV-OPC post-treatment includes a variety of frequent clinical and radiological examinations that are based on standard oncological surveillance protocols rather than being specific for HPV related disease, and does not currently include serologic or virologic testing.

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