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# Prospective assessment of multiple HPV-positive oropharyngeal squamous cell carcinomas

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Human Papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (HPV + OPSCC) is increasing in prevalence in the United States, as are cases of patients

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Declaration of Competing Interest

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with multiple HPV + OPSCCs (mHPV + OPSCC) [1]. Using retrospective institutional cohorts, systematic review and SEER database review our group has demonstrated that the prevalence of mHPV + OPSCCs is estimated to be 0.5–2.5% of HPV + OPSCC cases [1]. However, we, and others, have hypothesized that this prevalence rate likely underestimates the true rate of mHPV + OPSCCs due to a host of factors. First, current treatment approaches may unknowingly eradicate small second primary tumors. For example, most patients with HPV + OPSCC receive either primary, or adjuvant radiation to the oropharynx, which may treat synchronous occult cancers. In patients treated with surgery alone, "uninvolved" oropharyngeal subsites are often resected, including the contralateral tonsil in the setting of an ipsilateral tonsil cancer. In the setting of an p16+ metastatic carcinoma of unknown primary, pathologic workup may stop, or become less rigorous, once an index oropharyngeal tumor has been identified, thereby failing to recognize small second tumors if present. Furthermore, biases intrinsic to retrospective studies, such as lost linkage to previous cancer history, likely underestimate the true incidence of second primaries. Supporting this concept is data from our manuscript showing that if you allow one of the two cancers to have unknown HPV status, prevalence rates increase to a range of 1–10%. To test the hypothesis that the prevalence of mHPV + OPSCCs is higher than the current level set by our initial publication, we designed a prospective cohort study to assess the true prevalence of mHPV + OPSCCs.

All patients presenting to a single academic institution 10.1.2019–9.30.2020 with early stage HPV + OPSCC and undergoing work-up followed by transoral robotic surgery (TORS) for definitive treatment were enrolled in the study (n = 54). All cases underwent thorough review of past cancer history and review of outside pathology if known to have had a previous head and neck cancer. Following TORS, all tissue removed was submitted for pathologic evaluation and sectioning, which was reviewed by a head and neck pathologist including determination of HPV status by p16 IHC and/or HPV-specific testing. This approach deviated from traditional approaches in which: (1) pathologic assessment was halted once a primary tumor was identified and (2) contralateral tonsils were only grossly examined. All patients with tonsil cancer underwent elective contralateral tonsillectomy. Four cases of mHPV + OPSCCs were identified (4/54, 7.4% prevalence). Of these four cases, one was synchronous and three were metachronous (Table 1). Here, metachronous was defined as identification of the second tumor greater than six months from initial presentation. Two of the three metachronous secondary primary cancers were treated surgically and one with chemoradiotherapy. Across the full cohort, 23/54 (43%) of patients were treated with surgery alone, with all patients free of disease at mean follow up 5.3 months (range 0–14 months).

Second primary malignancies (SPM) contribute to a significant decrease in overall survival in patients with head and neck squamous cell carcinoma (HNSCC) and are the second leading cause of death in this patient population [2]. The prevalence of SPM in carcinogen-induced HNSCC has been found to be ~14%, although some studies show the lifetime risk is significantly higher [3,4]. While it has generally been assumed that patients with HPV + OPSCC are not at significant risk for multiple cancers, utilizing retrospective data, we, and others, have previously demonstrated a low but appreciable risk of more than one HPV-mediated cancer [1,5]. This single institution prospective cohort study supports our

hypothesis that the rate of mHPV + OPSCCs is higher than that reported from retrospective datasets, at 7.4%, and should serve as the new benchmark prevalence for mHPV + OPSCCs. As the incidence of HPV + OPSCCs continues to increase across the globe, and as deintensification with surgical treatment alone becomes more common, it is highly probable that the prevalence of mHPV + OPSCCs will increase further. Additional multi-institution prospective cohorts are needed to further confirm these findings, as are guidelines for treating mHPV + OPSCCs. Here in this prospective cohort, and in our previous work, mHPV + OPSCCs are most commonly detected either synchronously, or within close approximation (<1 year), suggesting that at a minimum, thorough and systematic interrogation of all oropharyngeal subsites should be undertaken before proceeding with treatment for HPV + OPSCCs.

Lastly, investigations into basic mechanisms of HPV infection in the oropharynx are greatly needed. Due in part to the lack of a known pre-malignant state in HPV + OPSCC, and thus the ability to study OPSCC at early stages of development, little is known regarding the natural history of oropharyngeal HPV infection and initial stages of malignant transformation. While our group has shown that mHPV + OPSCCs are caused by the same viral isolate, at the time of infection with HPV, it is unknown if one or multiple regions of the oropharynx become infected [6]. Similarly, while it is believed that re-infection from the same viral type can occur, it is unknown whether oropharyngeal tissue can be re-infected by the identical viral genome through repeated exposures (i.e., a lack of protective homologous immunity) [7]. The development of mHPV + OPSCCs, driven by the same viral isolate, suggests that infection either occurs at the same time in multiple locations, or repeat exposure to the same virus, (from the same partner), can lead to recurrent infections in multiple subsites. Regardless, more in-depth studies of HPV oropharyngeal infections are critically needed.

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## Table 1

Summary of clinical and pathologic characteristics for patients with mHPV + OPSCCs.

| **Patient** | **1** | **2** | **3** | **4** |
|---|---|---|---|---|
| Sex | M | F | M | M |
| Age* | 55 | 51 | 62 | 67 |
| First Tumor Location | Right Tonsil | Right BOT | Left Tonsil | Right Tonsil |
| Treatment | Surgery | Surgery | Surgery | Radiation |
| Size (cm)** | 1.8 | 1.7 | 2.7 | 0.8 |
| Adjuvant Treatment | Observation | Observation | Observation | NA |
| T Stage | 1 | 1 | 2 | 1 |
| N Stage | 1 | 1 | 1 | 1 |
| Second Tumor Location | Left BOT | Left BOT | Right Tonsil | Left BOT |
| Time Interval in Diagnosis | 8 Months | 7 Months | 0 | 6 Years |
| Treatment | Surgery | CRT | Surgery | Surgery |
| Size (cm)** | 2.3 | 0.35 | 0.45 | 2.8 |
| Chronicity | Metachronous | Metachronous | Synchronous | Metachronous |
| T Stage | 1 | 1 | 1 | 2 |
| N Stage | 1 | 0 | 1 | 0 |

Abbreviations: BOT: Base of Tongue, CRT: Chemoradiotherapy.

*Age at first diagnosis.

**Largest single dimension.