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Surveillance Imaging in HPV-related Oropharyngeal Cancer

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Abstract. *Background/Aim: Current guidelines derived from a pre-human papilloma virus (HPV) era in oropharyngeal cancer do not recommend routine surveillance imaging. We aimed to analyze the method of recurrence detection in HPV+ disease to determine a role for follow-up imaging. Patients and Methods: All HPV+ and* HPV– *oropharyngeal cancer patients treated at our institution from 2005-2016 with biopsy-proven recurrence were identified and their method of recurrence detection was analyzed. Results: A total of 16 HPV+ oropharyngeal cancer patients were identified to have recurrence, 12 (75%) of which experienced distant recurrence and 13 (81.3%) were detected asymptomatically with imaging at a median time of 19.7 months after initial treatment and verifying no residual disease. Twelve (75%) detections were with PET-CT. While* HPV– *patients (17 patients) also have a high rate of asymptomatic detection (16 patients, 94.1%), their 3-year post-recurrence survival was significantly lower at 6.5% compared to 83.6% for the HPV+ group ($p<0.01$). Conclusion: In HPV+ patients, a large proportion of failures are asymptomatic distant metastases, which occur beyond 6 months following treatment completion, and are detected with whole body imaging alone. In light of long term post-recurrence survival observed, this preliminary data suggests that routine surveillance imaging should be further studied for HPV+ disease.*

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Current treatment guidelines from the National Comprehensive Cancer Network (NCCN) (1) suggest one scan of the head and neck to be completed within 6 months after a patient completes treatment for their oropharyngeal cancer (OPC) without any recommendations for routine surveillance imaging in asymptomatic patients without a tobacco history. However, these guidelines are derived from data collected during a time in which the distinction between Human papilloma virus (HPV) positive and negative disease was not appreciated. In the HPV+ era, studies have suggested that in the United States, approximately 70% to 90% of newly diagnosed OPC are caused by HPV (2-4). It is well known that HPV status is an important prognostic indicator and that HPV+ tumors are distinct from HPV– tumors. Studies have shown that with standard therapy, the prognosis of patients with HPV+ OPC is markedly improved compared to HPV negative disease (5, 6).

Despite favorable survival characteristics, systemic recurrences occur in a significant fraction of HPV+ patients treated with loco-regional directed therapy and careful routine surveillance may be essential to the timely detection of recurrence. In fact, HPV+ OPC has been found to have comparable rates of distant metastasis (approximately 10-15%) as HPV– disease, despite being thought of as having favorable prognosis (7-9). Studies have suggested that HPV+ OPCs tended to recur with distant metastases, and present after a longer interval with a more disseminated metastasis or unusual pattern than HPV negative cancers (8, 10). This widespread metastasis pattern consists of an increased number of metastasis sites along with atypical organs presenting with recurrence. This raises the question about whether only one 6-month follow up scan is sufficient in the context of HPV+ disease, where long-term survival may be possible. We therefore investigated the mechanism of detection and time frame of recurrence to determine appropriate surveillance strategies in HPV+ OPC.

Materials and Methods

After receiving approval from the Icahn School of Medicine at Mount Sinai Institutional Review Board, all patients with HPV+ OPC who experienced biopsy proven recurrence detected and treated from 2005 to 2016 at our institution were identified. A comparison HPV– population was then identified from the same time period. Pathology reports were reviewed to determine the results of HPV testing. Patients with incomplete HPV status were excluded. At our institution, p16 IHC staining is performed on all oropharyngeal squamous cell carcinoma specimens submitted to pathology. If p16 staining meets criteria for positivity, then formal HPV PCR testing is then performed to confirm HPV positivity and to provide the high-risk viral serotype.

The records of patients with biopsy proven recurrence were reviewed to determine the means in which recurrence was detected. Patients frequently underwent salvage treatment such as additional surgery, chemotherapy, and radiation regiments after recurrence was proven. Clinical documentation and electronic medical records were reviewed to determine patient outcomes. Statistical analyses were completed in Microsoft Excel and R (version 2.15.2) with the survival package.

Results

Cohort characteristics. There was a total of 33 patients who met inclusion criteria for the study. 16 HPV+ OPC patients with biopsy proven recurrence were identified. Their median age was 55.5 years (range=45-70 years) with a median follow up of 42.5 months. Eight (50%) of these patients had a history of smoking. A comparison cohort of 17 HPV– OPC patients were identified with a median age of 59 years (range=52-83 years) and a median follow up time of 24.3 months. Thirteen (76.5%) of these patients had a history of smoking. Further patient characteristics, including staging, are given in Table I. Fisher's exact test was used to compare the groups and to determine *p*-values.

Method of recurrence detection. Median time from completion of initial treatment to recurrence detection was 19.7 months (range=5.3-194.8 months) for HPV+ group and 11.5 months (range=4.1-40.7 months) for HPV– group. Distribution of time to recurrence for both cohorts is displayed in Table II. A variety of methods were responsible for recurrence detection. They included PET-CT scan, CT scan with contrast, clinician physical exam and patient complaints. In HPV+ patients, 13 (81.3%) of 16 patients were asymptomatic upon recurrence detection; 12 of these recurrences were detected with PET-CT. Comparatively, in HPV– patients, 16 (94.1%) of 17 patients were asymptomatic at their time of recurrence; 13 of these recurrences were detected with PET-CT. Overall, PET-CT was the most common technique used to detect patient recurrence in our patient population. It was responsible for detecting 25 cases (75.8%) out of our total 33 patients in our study. Further details regarding detection method are shown in Table III.

Table I. *Patient characteristics*.

	HPV+ population (16 Total)	HPV– population (17 Total)	*p*-Value
Gender			0.235
Male	14 (87.5%)	12 (70.6%)	
Female	2 (12.5%)	5 (29.4%)	
Age (years)	Median 55.5, (range 45-70)	Median 59, (range 52-83)	0.687
Positive smoking history	8 (50%)	13 (76.5%)	0.114
TNM Staging			
Tumor			
Tx (unknown primary)	1 (6.25%)	0 (0%)	0.693
T1	3 (18.75%)	5 (29.4%)	
T2	8 (50%)	6 (35.3%)	
T3	1 (6.25%)	2 (11.8%)	
T4	3 (18.75%)	4 (23.5%)	
Nodes			
N0	3 (18.75%)	3 (17.6%)	0.760
N1	3 (18.75%)	3 (17.6%)	
N2	9 (56.25%) (8 N2b, 1 N2c)	11 (64.7%) (8 N2b, 3 N2c)	
N3	1 (6.25%)	0 (0%)	
Primary tumor location			
Base of tongue	6 (37.5%)	6 (35.3%)	0.417
Tonsil	8 (50%)	7 (41.2%)	
Oropharyngeal (unspecified)	1 (6.25%)	4 (23.5%)	
Unknown	1 (6.25%)	0 (0%)	

Recurrence patterns. In the HPV+ cohort, the majority (75%) of patients experienced distant recurrence. The most common site of recurrence was the lung, occurring in 8 of the 16 instances. Comparatively, a higher proportion of patients in the HPV– cohort experienced local recurrence, accounting for 10 (58.8%) of the 17 cases.

Post-recurrence outcomes. Median survival after recurrence was 18.4 months for HPV+ patients. All HPV+ patients underwent salvage therapy. Thirteen (81.3%) of the 16 HPV+ patients who recurred are still alive at a median time of 19.1 months after recurrence (range=4.1-68.6 months). Comparatively, 12 (70.6%) of 17 HPV– OPC patients underwent salvage therapy. Post-recurrence salvage treatments are shown in Table IV. Patients who did not undergo salvage therapy received either palliative treatment or deceased before the initiation of salvage treatment. HPV– OPC recurrences were not salvaged as successfully as the HPV+ recurrences, despite comparable rates of early asymptomatic detection in both groups. Fifteen (88.2%) of the 17 total patients in the HPV– group deceased after recurrence. Median survival after recurrence was 11.7 months for HPV– patients. The two patients alive from the

Table II. *Distribution of time to recurrence.*

Time (months)	HPV+ (16 total)	HPV– (17 total)
0-6	1 (6.3%)	2 (11.8%)
6-12	1 (6.3%)	7 (41.2%)
12-24	8 (50%)	4 (23.5%)
24-36	2 (12.5%)	3 (17.6%)
36+	4 (25%)	1 (5.9%)

Table III. *Recurrence detection method.*

	HPV+ (16 Total)	HPV– (17 Total)
Asymptomatic	13 total (81.25%)	16 total (94.1%)
PET-CT	12 (75%)	13 (81.25%)
CT with contrast	1 (6.25%)	2 (12.5%)
Physical exam	0 (0%)	1 (6.25%)
Symptomatic	3 total (18.75%)	1 total (5.9%)
Patient complaints	3 (18.75%)	1 (5.9%)

HPV– cohort were all detected with PET-CT scan and have survived for 9.8 and 43.4 months after recurrence. 3-year post recurrence survival was 83.6% (95%CI=64.9-100%) in HPV+ group and 6.5% (95%CI=1.0-43.3%) ($p<0.01$) in HPV– group.

Table IV. *Post-recurrence salvage treatment.*

Salvage treatment	HPV+ (16 Total)	HPV– (17 Total)
Surgery + Adjuvant radiation	1 (6.3%)	1 (5.9%)
Surgery + Adjuvant chemoradiotherapy	5 (31.3%)	3 (17.6%)
Chemoradiotherapy	5 (31.3%)	4 (23.5%)
Chemotherapy	5 (31.3%)	4 (23.5%)
Palliative treatment	0 (0%)	2 (11.8%)
None	0 (0%)	3 (17.6%)

Discussion

This study suggests that the majority of HPV+ OPC recurrences were asymptomatic, clinically inappreciable distant metastases, which are detected with routine surveillance imaging only. Importantly, the majority of these recurrences occurred beyond 6 months after an initial post-treatment scan did not reveal any evidence of disease. Despite disease recurrence, long term survival and even possible cure were possible in the HPV+ cohort after undergoing salvage therapy (11). In contrast, regardless of how recurrences were detected in HPV– group, long term survival was extremely unlikely.

Current NCCN guidelines recommend imaging of the head and neck within 6 months of treatment completion without any recommended screening for distant metastases. These guidelines are based on data from a pre-HPV era. Our data suggest that HPV+ patients present with recurrence after a longer time interval, despite initial negative scan, and have long term survival. The median time to recurrence was 19.7 months for HPV+ patients, compared to 11.5 months for HPV– patients. With awareness and instances of HPV+ disease on the rise, the possibility of later recurrences in HPV+ OPC could be significant and a re-evaluation of current surveillance guidelines may be necessary for this subgroup.

We are also beginning to appreciate that HPV+ disease metastasizes in a unique pattern distinct from HPV– disease. Our series is consistent with the literature, which suggests that the distant metastasis rate in HPV+ disease remains high (7, 12, 13) despite a very high rate of local control. Furthermore, while the lungs represent a frequent site of metastasis, soft tissue and visceral organs represent sites of HPV+ metastasis which are distinct from HPV negative disease. To treat HPV+ OPC patients, multimodality aggressive therapy may benefit those with recurrence (14). Early detection for distant metastases can be difficult to detect without imaging, because they initially present asymptomatically. Figure 1 shows examples of asymptomatic HPV+ OPC recurrences detected with PET-CT imaging. HPV+ patients had a wide variety of primary tumor stages and locations; those from all stages, including early, appear to be recurring. As a result, it can be difficult to reliably predict recurrence patterns based on initial disease.

PET-CT imaging has emerged in recent years as a less invasive and equally effective method to monitor patients compared to bilateral neck dissection (15). PET-CT surveillance along with early recurrence detection have changed the management of disease significantly (16, 17). However, there is concern about false positive rates and subsequent unnecessary biopsies, particularly in the head and neck after radiation (18, 19). Regardless, the sensitivity of imaging such as PET-CT remains high in detecting recurrent disease (16, 18, 20, 21) and establishing comparison images over time allows for increased accuracy (22). Furthermore, studies have suggested that surveillance imaging remains cost effective and beneficial, due to its less invasive nature and high efficacy (23, 24). In the past with HPV– head and neck cancers, early detection of distant metastasis may not have been clinically relevant given its rapid progression. However, the biology of HPV+ disease may be such that early detection is essential and risks associated with surveillance imaging are outweighed by the benefits,

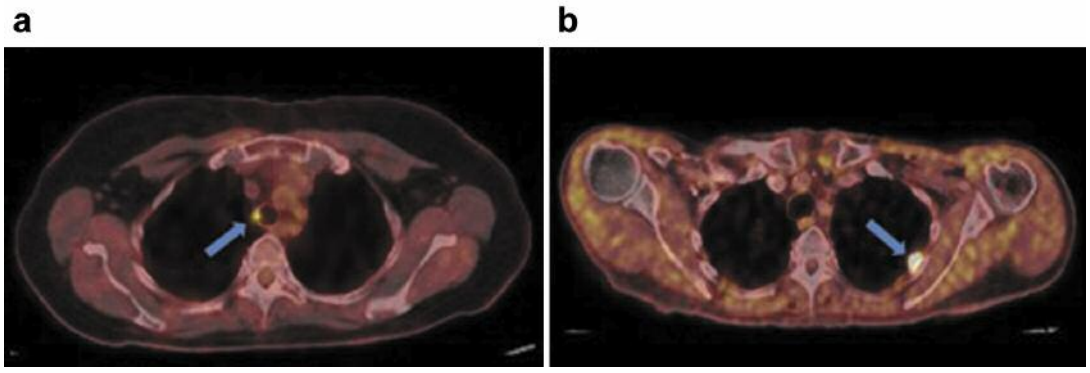

Figure 1. *Cases of Asymptomatic HPV+ Recurrence Detection with PET-CT. Surveillance imaging such as PET-CT allows for detection of abnormalities that can be difficult to pick up symptomatically or on conventional physical exam. a) Distant asymptomatic trachea recurrence. b) Distant lung metastasis.*

allowing for additional options for systemic therapy. Further study is required to determine the significance of early detection and how it affects salvage treatment options and translates to long term survival benefits. This analysis was not possible in our patient population because most of the recurrences were detected early with imaging at a time when patients did not experience clinical symptoms.

The limitations of this study include its retrospective nature, small sample size, and lack of standardization of surveillance imaging. This study is not powered to observe differences in survival or outcomes based on recurrence pattern. Additionally, this study was not designed to evaluate the false positive rates and unnecessary biopsies that are the result of routine surveillance imaging protocols. Additionally, median follow up time in the HPV+ group was 42.5 compared to 24.3 months in HPV– group. The longer follow-up time in the HPV+ group can be attributed to a few factors: later recurrence of disease along with longer overall survival.

The role of distant surveillance imaging for HPV+ disease is evolving. At our institution, we routinely perform surveillance imaging beyond 6 months, which typically include at least one annual PET-CT scan at the treating physician's discretion. Given the limitations of our data, we do not propose changing the current NCCN guidelines regarding screening; however, our data should provide preliminary evidence and rationale to explore surveillance imaging in this more favorable cohort. We propose future prospective studies to investigate the optimal timing, imaging modality, and potential clinical benefit to early detection of recurrence as our retrospective study was not powered to do so. The data driving the current recommendations are predominantly derived from the pre-HPV epidemic era. Just as treatment paradigms are shifting for HPV+ *vs*. HPV– disease, the surveillance guidelines should be updated as well.

In summary, the results from this study suggest that the majority of recurrences in HPV+ OPC occur distantly beyond 6 months following treatment completion and are subjectively and clinically undetectable. Given the potential for long term post-recurrence survival in HPV+ patients, early detection with surveillance imaging at a time of minimal systemic disease burden may be beneficial, although further investigation is warranted. Our study provides preliminary data to further investigate the role and timing of whole body surveillance imaging for HPV+ cancers.

Conflicts of Interest

None.

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