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Influence of Smoking History on Imaging Characteristics among HPV-Positive Oropharyngeal Cancer Patients: A Blinded Matched-Pair Analysis

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Abstract

Background and Purpose—Human papillomavirus (HPV)-positive oropharyngeal cancers represent a distinct clinical entity with more favorable prognosis than HPV-negative oropharyngeal cancers. However, among patients with HPV-positive oropharyngeal carcinomas, those with a significant smoking history have a much worse prognosis. Recently, imaging characteristics of oropharyngeal cancers were identified as markers of poor prognosis. The purpose of this study was to determine whether nodal imaging characteristics differ between smokers and never/light smokers with HPV-positive oropharyngeal cancer.

Materials and Methods—Review of 130 pretreatment CT examinations of HPV-positive oropharyngeal cancers in smokers (>10 pack-years) and never/light smokers (≤10 pack-years) matched for T stage and tumor subsite was performed with the reviewing radiologist blinded to HPV status, smoking history, and clinical stage. An additional 24 pretreatment CT examinations of patients with HPV-negative oropharyngeal cancers were also reviewed in a blinded fashion. Imaging characteristics of metastatic nodal disease were compared using chi-square testing (Fisher exact testing where appropriate) and McNemar chi-square testing for the matched-pair analysis.

Results—As expected, those with HPV-positive oropharyngeal cancer were more likely to be younger, male, non-Hispanic white, never/former smokers, and never drinkers than those with HPV-negative oropharyngeal cancer. Furthermore, the HPV-positive oropharyngeal cancers were more likely to be in the tonsil, smaller T-category, higher N-category, poorly differentiated, tonsil

primaries, smaller T-category, higher N-category, and poorly differentiated than HPV-negative oropharyngeal cancers. However, among the HPV-positive oropharyngeal cancers, we could identify no obvious difference in the pretreatment imaging characteristics of paired smokers and never/light smokers.

Conclusions—Among patients with HPV-positive oropharyngeal cancer, no imaging characteristics were identified to correlate with the critical prognostic feature smoking status. Cystic and necrotic nodal metastases, as described previously, were more common among patients with HPV-positive than HPV-negative oropharyngeal cancers. While cystic nodal metastases were more common among never/light smokers with HPV-positive oropharyngeal cancer than smokers with HPV-positive oropharyngeal cancer; however, because these results did not reach statistical significance, we conclude that imaging results cannot serve as a surrogate for an HPV-driven phenotype.

INTRODUCTION

As smoking prevalence within the United States has decreased, there has been a resultant decreased age adjusted incidence of oral cavity, hypopharyngeal and laryngeal carcinomas. Conversely, the age adjusted incidence of oropharyngeal carcinoma, has increased during this same period secondary to (HPV)-related squamous cell carcinoma of the oropharynx (SCCOP).¹⁻⁷ While the proportion of oropharyngeal carcinomas potentially attributable to HPV varies among geographic regions worldwide, within the U.S. population at least 60% of oropharyngeal cancers are potentially attributable to HPV.⁸⁻⁹

Among patients with SCCOP, HPV status and smoking status are perhaps the most important independent prognostic factors.¹⁰ Through analysis of data collected by the Radiation Therapy Oncology Group (the RTOG 0129 study), Ang et al¹⁰ evaluated the prognostic significance of smoking among patients with stage III and IV HPV-positive and HPV-negative SCCOP who presented without distant metastases. Recursive partitioning analysis was utilized to stratify patients with oropharyngeal cancer into low-risk (3-year overall survival rate of 93.5%), intermediate-risk (3-year overall survival rate of 67.0%), and high-risk (3-year overall survival rate of 41.6%) categories. The most significant determinants of overall survival were HPV status (inferred from p16 positivity), followed by smoking status (<10 pack-years versus >10 pack-years), and finally N category for patients with HPV-positive SCCOP and T category for patients with HPV-negative SCCOP.^{10,11} It is now presumed that a HPV-positive SCCOP arising in someone with limited smoking history has a phenotype driven by HPV rather than tobacco carcinogens, while a HPV-positive SCCOP arising in a smoker is driven both by HPV and a host of mutations caused by tobacco carcinogens, and those tumors with an HPV driven tumor phenotype have a much better prognosis.^{4,10,11} The molecular profile signifying an HPV driven tumor phenotype is characterized by high HPV titer, increased p16 expression, wild-type *p53*, and low epidermal growth factor receptor (EGFR) expression.¹²⁻¹³ However, smokers likely have a worse overall prognosis relative to nonsmokers with HPV-positive SCCOP due to somatic alterations related to tobacco exposures including mutated *p53* and EGFR overexpression and likely many others.¹³

Recently, Spector et al¹⁴ described the presence of matted nodes visible on pretreatment CT examination as a poor prognostic indicator associated with future development of distant metastases in patients with SCCOP. Matted nodes were more commonly identified among patients with HPV-negative SCCOP compared to those with HPV-positive SCCOP.¹⁴ We recently described differences in pretreatment CT imaging characteristics between patients with HPV-positive and HPV-negative SCCOP in a blinded matched-pair analysis, reporting increased invasion of adjacent muscles at the primary tumor site of HPV-negative SCCOP and increased frequency of cystic nodal metastases in those with HPV-positive SCCOP.¹⁵ In light of the major prognostic significance of smoking status among patients with HPV-positive SCCOP, we hypothesized that imaging differences between smokers and nonsmokers may aid in identifying the subset of patients harboring an HPV-driven tumor phenotype (believed to occur most often in nonsmokers/light smokers). We therefore investigated whether smokers have different nodal imaging characteristics than never/light smokers among patients with HPV-positive oropharyngeal cancer.

MATERIALS AND METHODS

Patients with a newly diagnosed SCCOP, who had been prospectively enrolled in an Institutional Review Board-approved molecular epidemiology study conducted between May 1995 and June 2008, were eligible for the current study. All patients in the parent molecular epidemiological study had met the following criteria: newly diagnosed, previously untreated SCCOP; resident of the United States; age greater than 17 years; no evidence of distant metastases; and no prior malignancy (excepting nonmelanoma skin cancer). Exclusion criteria for this imaging study were treatment of a head and neck malignancy (conventional surgical management, radiotherapy, or chemoradiation) prior to the CT examination. Patients were also excluded if contrast-enhanced pretreatment CT imaging was not available.

HPV status was determined by HPV insitu hybridization and p16 expression by immunohistochemistry. SCCOPs were considered HPV positive if both HPV in situ hybridization was positive and p16 was overexpressed, and tumors were considered HPV negative if both HPV in situ hybridization and p16 immunohistochemistry were negative. “Never smokers” were defined as having smoked fewer than 100 cigarettes in their lifetime. “Light smokers” were defined as those with less than or equal to 10 pack-years of cigarette smoking. “Smokers” were defined as those with cigarette smoking exposure greater than 10 pack-years. “Current drinkers” were defined as having at least one alcoholic drink per week for at least 1 year and who were still drinking in this manner at the time of their presentation. “Former drinkers” were defined as those who drank alcoholic beverages in this manner in the past but had begun drinking less or stopped drinking at least 1 year before presentation. T category was determined by clinical exam, including direct and indirect transoral visual inspection, palpation, direct laryngoscopy, and pretreatment imaging.

Retrospective review of pretreatment CT examinations of paired HPV-positive SCCOP in smokers and never/light smokers matched for T category and tumor subsite was performed by a single neuroradiologist blinded to HPV status, smoking status, and clinical stage. Additionally, 24 pretreatment CT examinations of HPV-negative SCCOP (23 were smokers,

1 never/light smoker) was performed in a similar blinded fashion; however, these patients were not matched, and thus matched-pair analysis of these patients was not performed.

All CT examinations were performed on GE scanners (16- and 64-channel systems, various software platforms, GE Healthcare Systems, Milwaukee, WI). Images were obtained after administration of intravenous contrast (125 ml, 60-sec delay) from the aortic arch to the orbital roof with the following imaging parameters: tube current 100–600 mA, tube voltage 120 kVp, gantry rotation time 0.5–1 sec, pitch 0.9, image thickness 1.25 mm). All patients with dental fillings had an additional stack of axial images obtained to angle away from the fillings. Although contrast bolus timing and volume of contrast may modify conspicuity of the interface between the primary lesion and surrounding soft tissues, in all cases contrast enhancement was sufficient to identify and adequately evaluate the primary tumor.

Imaging variables of the cervical lymphatics compared included radiologic N stage, presence of cystic nodes, necrotic nodes, matted nodes, extracapsular spread, and level 4 and/or supraclavicular lymph nodes. Extracapsular spread was recognized by indistinct nodal margins, irregular nodal capsular enhancement, and infiltration into the adjacent perinodal fat or muscle. Matted nodes were defined as 3 adjacent nodes abutting one another with extracapsular spread and loss of an intervening fat plane. Cystic lymph nodes were defined as having a thin (<2 mm) enhancing capsule and homogeneous fluid content (>70% with Hounsfield units <20), with no internal complexity. Necrotic nodal metastases were defined as having thicker or more irregular walls with complex central low attenuation. Demographic and clinical characteristics and imaging characteristics of metastatic nodal disease were compared using chi-square testing (Fisher exact testing where appropriate) and McNemar's chi-square test for the matched-pair analysis.

RESULTS

Of 77 matched pairs of patients with HPV-positive SCCOP identified, 12 pairs were excluded because one or both members of the pair had no pretreatment CT available for review; consequently, 65 matched pairs (130 patients with an HPV-positive SCCOP) were included in the analysis. An additional 27 patients were identified with a HPV-negative SCCOP, and of these 3 patients were excluded because no pretreatment CT scan was available for review, yielding 24 patients with HPV-negative SCCOP for review.

Demographic and clinical characteristics of patients with HPV-positive SCCOP (combined smokers and never/light smokers) and non-matched patients with HPV-negative SCCOP are presented in Table 1. As expected, the patients with HPV-positive SCCOP were more likely to be younger, male, non-Hispanic white, never/former smokers, and never drinkers than those with a HPV-negative SCCOP, though not all of these differences were statistically significant. Also expected, patients with HPV-positive SCCOP had smaller and more poorly differentiated primary tumors and a trend toward higher N-category disease at presentation compared with patients with HPV-negative SCCOP. On blinded review of pretreatment CT scans and similar to previous publication¹⁵, nodal metastases were more likely visible and more likely cystic for those with an HPV-positive SCCOP than those with an HPV-negative SCCOP (Table 1).

Demographic and clinical characteristics were similar among smokers and never/light smokers with HPV-positive SCCOP matched for T category and tumor subsite (Table 2). Nodal imaging characteristics of HPV-positive SCCOP in smokers and never/light smokers are presented in Table 3. There were no statistically significant differences in the pretreatment imaging characteristics of nodal metastases between matched paired smokers and never/light smokers with HPV-positive oropharyngeal cancer, including matted nodes (Fig 1), though smokers were less likely to have cystic metastases (Fig 2) than never/light smokers (Fig 3) (18% vs. 27%).

The matched-pair analysis of the nodal imaging characteristics of patients with HPV-positive SCCOP (smokers vs. never/light smokers) is presented in Table 4. Twelve matched pairs were excluded from nodal analysis secondary to one or both members of the pair had no nodes visible on CT imaging. This matched-pair analysis revealed no significant difference in the pretreatment CT imaging characteristics of nodal metastases between smokers and never/light smokers with HPV-positive SCCOP.

DISCUSSION

In this blinded matched-pair analysis of differences in pretreatment CT imaging between smokers and never/light smokers with HPV-positive SCCOP, we could identify no significant difference in imaging characteristics of nodal metastases, including incidence of matted nodes, cystic nodal metastases, and necrotic nodes. Despite the relatively poor prognosis of smokers with HPV-positive SCCOP relative to never/light smokers, we observed no significant difference in the incidence of extracapsular spread of nodal metastases, a well-established predictor of poor prognosis in traditional squamous cell carcinoma of the head and neck.^{16–19}

Cystic nodal metastases, which we previously found more commonly among HPV-positive SCCOP relative to HPV-negative SCCOP, are a unique pathologic and histologic entity with corresponding characteristic imaging appearance.²⁰ However, in matched-pair analysis, we found no significant increased incidence of cystic nodal metastases among never/light smokers with HPV-positive SCCOP relative to smokers. Thus, while the formation of cystic nodal metastases is more common in HPV-positive SCCOP relative to HPV-negative SCCOP, in our analysis cystic nodal metastases were not an imaging surrogate for the HPV-driven tumor phenotype (ie HPV-positive SCCOP in those lacking smoking exposures). Recently, Dahlstrom et al²¹ demonstrated a need to revise the current TNM staging system for SCCOP to include HPV and smoking status. Unfortunately, there do not appear to be any obvious imaging characteristics among HPV-positive SCCOP nodal metastases that can differentiate between never/light smokers harboring an HPV-driven tumor phenotype and smokers with this disease.

Demographic (middle-aged non-Hispanic white males with less smoking) and clinical trends (lower T category, higher N category, and poorly differentiated tumors) of our HPV-positive SCCOP population (smokers and never/light smokers) relative to HPV-negative SCCOP were consistent with the established literature.^{21–25} In keeping with prior analysis,¹⁵ we found overall increased incidence of cystic nodal metastases among HPV-positive SCCOP

compared to HPV-negative SCCOP, although these results were not statistically significant in the current study. With the changing demographics of SCCOP related to HPV, cystic neck masses in an adult patient should be considered cystic nodal metastases until proven otherwise, despite relatively young age, lack of significant smoking history, or lack of visualization of the primary lesion.^{4,10,26} Given the improved overall prognosis of patients with HPV-positive SCCOP relative to patients with HPV-negative SCCOP, it is important to identify patients with HPV-positive tumors. The radiologist may prompt referral to a head and neck surgeon by suggesting the presence of radiologic and clinically occult primary tumor as well as recommending that cystic nodal metastases be tested for HPV. Although reports are not entirely consistent within the literature primarily due to restrictive stage inclusion criteria among prospective trials, our data are consistent with the overall trend of HPV-positive SCCOP presenting for treatment with an earlier T category and more advanced N category related to HPV-negative SCCOP.^{10,11,27–28}

The most significant limitation of our study was our sample size. Specifically, the small sample size of the HPV-negative population available for this analysis precluded matched pairing of patients with HPV-negative SCCOP to the matched smokers and never/light smokers with HPV-positive SCCOP. However, despite the lack of matched pairing, cystic nodal metastases were still more common among HPV-positive patients, which concurs with a prior, more robust matched-pair analysis of differences in pretreatment CT characteristics of HPV-positive SCCOP relative to HPV-negative SCCOP. Despite limitations imposed by the small sample size, matched-pair analysis provides a controlled and homogeneous setting and is a well-established means of controlling for confounding. Furthermore, all images were reviewed specifically for this study by a single radiologist without knowledge of patients' HPV or smoking status. An additional limitation of our study was its retrospective design. However, this study did include robust inclusion criteria for HPV-positive (both in situ hybridization and p16 positive) and HPV-negative (both in situ hybridization and p16 negative) status.

CONCLUSIONS

Pretreatment CT of SCCOP among never/light smokers and smokers with HPV-positive SCCOP did not demonstrate significant differences in incidence of cystic nodal metastases, necrotic nodal metastases, extracapsular spread, or matted nodes. Thus, cystic nodal metastases, which were previously shown to occur more commonly among HPV-positive SCCOPs, are not an imaging surrogate for the HPV-driven phenotype found more commonly among HPV-positive never/light smokers, with improved overall survival. HPV-positive SCCOPs were more likely to spawn cystic nodal metastases relative to HPV-negative SCCOPs, although these results were not significant, likely related to small sample size. No characteristic of nodal metastases was identified in HPV-positive never/light smokers compared to HPV-positive smokers to identify those harboring the HPV-driven tumor phenotype, which is associated with increased overall survival.

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Fig 1.
HPV-positive SCCOP in a smoker demonstrating matted lymphadenopathy. Axial contrast-enhanced CT image shows matted lymphadenopathy in level IIa.

Fig 2.
HPV-positive SCCOP in a smoker demonstrating cystic nodal metastasis. Axial contrast-enhanced CT image shows predominantly cystic mass in level IIa.

Fig 3.
HPV-positive SCCOP in a never/light smoker demonstrating cystic nodal metastasis. Axial contrast-enhanced CT image shows predominantly cystic mass in level IIb.

Table 1

Demographic and clinical characteristics of patients with HPV-positive SCCOP and HPV-negative SCCOP.

Variable	HPV-positive SCCOP (N = 130)		HPV-negative SCCOP (N = 24)		P Value [*]
	No.	(%)	No.	(%)	
Age category					0.081
< 55 years	63	(48.5)	7	(29.2)	
55 years	67	(51.5)	17	(70.8)	
Sex					0.001
Male	113	(86.9)	14	(58.3)	
Female	17	(13.1)	10	(41.7)	
Race/ethnicity					0.061
Non-Hispanic white	112	(86.2)	17	(70.8)	
Other	18	(13.8)	7	(29.2)	
Smoking status					0.001
Current smoker	37	(28.5)	16	(66.7)	
Former smoker	51	(39.2)	7	(29.2)	
Never smoker	42	(32.3)	1	(4.1)	
Alcohol drinking status					0.067
Current drinker	64	(49.2)	9	(37.5)	
Former drinker	29	(22.3)	11	(45.8)	
Never drinker	37	(28.5)	4	(16.7)	
Tumor subsite					0.290
Tonsil	80	(61.5)	12	(50.0)	
Base of tongue	50	(38.5)	12	(50.0)	
Tumor category					0.006
T1	36	(27.6)	3	(12.5)	
T2	56	(43.1)	5	(20.8)	
T3	20	(15.5)	9	(37.5)	
T4	18	(14.0)	7	(29.2)	
Nodal category					0.079
N0-1	23	(17.7)	8	(33.3)	

Variable	HPV-positive SCCOP (N = 130)		HPV-negative SCCOP (N = 24)		P Value*
	No.	(%)	No.	(%)	
N2-3	107	(82.3)	16	(66.6)	0.656
Stage					
I-II	8	(6.2)	2	(8.3)	
III-IV	122	(93.8)	22	(91.7)	
Grade#					0.024
Well differentiated	5	(4.2)	4	(18.2)	
Moderately differentiated	37	(31.1)	9	(40.9)	
Poorly differentiated	77	(64.7)	9	(40.9)	
Nodes visible on CT					0.486
Yes	116	(89.2)	20	(83.3)	
No	14	(10.8)	4	(16.6)	0.566
Cystic nodes present on CT					
Yes	26	(22.4)	3	(15.0)	
No	90	(77.6)	17	(85.0)	

* Chi-square test except where a cell had fewer than 5 observations, in which case Fisher exact test was used.

Grade was not recorded in 11 HPV+ and 2 HPV- cases. For this analysis, moderately well-differentiated tumors (1 HPV+ and 1 HPV-) were included in the well-differentiated group and moderately poorly differentiated (7 HPV+ and 0 HPV-) were included in the poorly differentiated group.

Table 2

Demographic and clinical characteristics of never/light smokers (10 pack-years) with HPV-positive SCCOP and smokers (>10 pack-years) with HPV-positive SCCOP and matched on T category and tumor subsite.

Variable	Never/Light Smokers with HPV-positive SCCOP (N = 65)		Smokers with HPV-positive SCCOP (N = 65)		P Value*
	No.	(%)	No.	(%)	
Age category					0.219
< 55 years	35	(53.8)	28	(43.1)	
55 years	30	(46.2)	37	(56.9)	
Sex					0.193
Male	54	(83.1)	59	(90.1)	
Female	11	(16.9)	6	(9.9)	
Race/ethnicity					0.612
Non-Hispanic white	55	(84.6)	57	(87.7)	
Other	10	(15.4)	8	(12.3)	
Smoking status					<0.001
Current smoker	5	(7.7)	32	(49.2)	
Former smoker	18	(27.7)	33	(50.8)	
Never smoker	42	(64.6)	0	(0.0)	
Alcohol drinking status					0.819
Current drinker	33	(50.8)	31	(47.7)	
Former drinker	13	(20.0)	16	(24.6)	
Never drinker	19	(29.2)	18	(27.7)	
Tumor subsite [†]					1.0
Tonsil	40	(61.5)	40	(61.5)	
Base of tongue	25	(38.5)	25	(38.5)	
Tumor category [‡]					1.0
T1	18	(64.3)	18	(27.7)	
T2	28	(43.1)	28	(43.1)	
T3	10	(15.4)	10	(15.4)	
T4	9	(13.8)	9	(13.8)	

Variable	Never/Light Smokers with HPV-positive SCCOP (N = 65)		Smokers with HPV-positive SCCOP (N = 65)		P Value*
	No.	(%)	No.	(%)	
Nodal category					0.818
N0-1	11	(16.9)	12	(18.5)	
N2-3	54	(83.1)	53	(81.5)	
Stage					0.718
I-II	5	(7.7)	3	(4.6)	
III-IV	60	(92.3)	62	(95.4)	
Grade [#]					0.584
Well differentiated	1	(1.6)	3	(5.3)	
Moderately differentiated	20	(32.8)	17	(29.8)	
Poorly differentiated	40	(65.6)	37	(64.9)	

[#]Grade was not recorded in 8 HPV+ smokers and 4 HPV+ never/light smokers. For this analysis, moderately well-differentiated tumors (0 HPV+ smokers and 1 HPV+ never/light smoker) were included in the well differentiated group and moderately-poorly differentiated (n=2 HPV+ smokers and 5 HPV+ never/light smokers) were included in the poorly differentiated group.

* Chi-square test except where a cell had fewer than 5 observations, in which case Fisher exact test was used.

[†]Matched variables (tumor subsite and T category).

Table 3
Imaging characteristics of nodal metastases among never/light smokers (10 pack-years) with HPV -positive SCCOP and smokers (>10 pack-years) with HPV -positive SCCOP

Variable	Never/Light Smokers HPV -positive SCCOP (N = 65)		Smokers with HPV -positive SCCOP (N = 65)		P Value*
	No.	(%)	No.	(%)	
Nodes visible					0.258
Yes	56	(86.2)	60	(92.3)	
No	9	(13.8)	5	(7.7)	
Cystic nodes present					0.275
Yes	15	(26.8)	11	(18.3)	
No	41	(73.2)	49	(81.7)	
Necrotic nodes present					0.865
Yes	46	(82.1)	50	(83.3)	
No	10	(17.9)	10	(16.7)	
Level 4 and/or supraclavicular nodes present					0.365
Yes	4	(7.1)	8	(15.4)	
No	52	(92.9)	52	(84.6)	
Extracapsular spread present					0.897
Yes	24	(42.9)	25	(41.7)	
No	32	(57.1)	35	(58.3)	
Radiologic N stage					0.504
N0-N1	14	(21.5)	11	(16.9)	
N2-N3	51	(78.5)	54	(83.1)	
Matted nodes present					0.862
Yes	24	(47.0)	25	(46.3)	
No	26	(53.0)	29	(53.7)	
Matted nodes present with extracapsular spread					1.000
Yes	20	(83.3)	21	(84.0)	
No	4	(16.7)	4	(16.0)	

Table 4

Matched-pair analysis of imaging characteristics associated with smoking status among HPV-positive patients.

Matched Pairs			Imaging Finding associated with Smoking (95% Confidence Interval)	P Value*
Smokers with HPV-positive SCCOP	Never/Light Smokers with HPV-positive SCCOP	Imaging Finding Present		
		Imaging Finding Absent		
<u>Nodes Visible (65 pairs)</u>				
Yes	53	3		
No	7	2	0.42 (0.07–1.88)	0.206
<u>Metastatic Lymph Nodes Cystic (53 pairs)</u>				
Yes	29	11		
No	13	0	0.85 (0.34–2.05)	0.683
<u>Metastatic Nodes Necrotic (53 pairs)</u>				
Yes	38	7		
No	5	3	1.40 (0.38–5.59)	0.564
<u>Level 4 and/or Supraclavicular Nodes (53 pairs)</u>				
Yes	1	7		
No	4	41	1.75 (0.44–8.15)	0.366
<u>Metastatic Lymph Nodes with ECS (53 pairs)</u>				
Yes	8	13		
No	14	18	0.92 (0.40–2.13)	0.847
<u>Matted Nodes Present (45 pairs)</u>				
Yes	9	12		
No	12	12	1.00 (0.41–2.43)	1.000

ECS=extracapsular spread.