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Association between High-Risk HPV and Radiological Findings in Oropharyngeal and Hypopharyngeal Squamous Cell Carcinoma

Gupta A.[1], Jain V.[2], Mandloi V.[3], Thomas T.[4], Sharma H.[1], Bonam J.[1], Gaikwad R.[1], Dongargaonkar P.[1], Mandalia V.[1], Israr F.[1]

[1]*Junior Resident, Department of Radiation Oncology, DBVP Rural Medical College, PIMS, Loni, Maharashtra, India.*

[2]*Professor & Head, Department of Radiation Oncology, DBVP Rural Medical College, PIMS, Loni, Maharashtra, India.*

[3]*Assistant Professor, Department of Radiation Oncology, DBVP Rural Medical College, PIMS, Loni, Maharashtra, India.*

[4]*Senior Resident, Department of Radiation Oncology, DBVP Rural Medical College, PIMS, Loni, Maharashtra, India.*

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ABSTRACT:

Background: Oropharyngeal and hypopharyngeal squamous cell carcinoma (OPHSCC) represent a significant subset of head and neck cancers, with a rising incidence linked to high-risk human papillomavirus (HPV) infections. Radiological imaging is pivotal in the evaluation and management of these cancers.

Objective: This study investigates the correlation between high-risk HPV status and specific radiological features in patients with OPHSCC, aiming to enhance diagnostic accuracy and treatment strategies.

Material and Methods: This descriptive observational study was conducted from June 2022 to May 2024 with ethical approval and informed consent from all participants. It included 52 patients diagnosed with oropharyngeal and hypopharyngeal squamous cell carcinoma (OPHSCC), who underwent histopathological examination and HPV testing. Comprehensive radiological imaging (CT and/or MRI) was performed, analyzing key features such as primary tumor size, location, volume, and extent, as well as the presence and size of lymph node metastasis. Characteristics of the largest lymph node, including whether it was predominantly solid or cystic and whether it had well-defined or irregular margins, were also examined. The study aimed to identify associations between these radiological and histopathological features and HPV positivity to explore predictive markers for HPV-mediated OPHSCC in resource-limited settings where HPV testing is unavailable.

Results: The majority of patients in this study were aged 51-60 years, with mean ages of 61 years for OPHSCC, 65 years for HPV-positive tumors, and 60 years for HPV-negative tumors, indicating a higher prevalence of HPV-mediated SCC in older adults. The study had a higher prevalence of male patients (82.69%) and a predominantly rural demographic (84.62%). Substance abuse was common (93%), with smoked tobacco combined with alcohol being the most frequent form. Clinically, the oropharynx was the most common site (55.78%). Radiologically, the mean tumor volume was 16.76 cm^3 for HPV-positive and 21.37 cm^3 for HPV-negative patients. HPV-positive patients had a mean nodal volume of 40.41 cm^3 compared to 21.12 cm^3 for HPV-negative patients. Significant differences were found in nodal margins ($p = 0.0372$), with HPV-positive patients having more well-defined margins, and in nodal consistency ($p = 0.0402$), where HPV-positive patients were more likely to have cystic nodes, while HPV-negative patients had more solid nodes.

Conclusion: Specific radiological features, notably cystic nodal metastases and well-defined nodal margins, are significantly associated with high-risk HPV status in OPHSCC. These findings support the integration of radiological imaging in the diagnostic workflow for HPV-mediated cancers.

Keywords: Human Papilloma Virus (HPV), Oropharyngeal cancer, Hypopharyngeal cancer, Radiological imaging, Cystic Nodal metastases, Nodal margins.

I. INTRODUCTION:

Head and neck cancer, the sixth most prevalent cancer globally, includes tumors originating from the oral cavity, oropharynx, larynx, hypopharynx, and sinonasal tract. Squamous cell carcinomas (SCC) account for around 90% of head and neck cancers (HNC). Traditionally linked to smoking and alcohol use, Human Papillomavirus (HPV) infection has

emerged in the past decade as a major etiological factor**(1)**, particularly for oropharyngeal squamous cell carcinoma (OPSCC). The incidence of HPV-positive OPSCC has risen significantly, with a global prevalence of 33% in 2021, varying geographically from 0% in southern India to 85% in Lebanon**(2)**. HPV-positive status correlates with a favorable prognosis and better response to chemoradiotherapy**(2)**.The oropharynx is the primary site where a clear etiological relationship exists between SCC development and chronic high-risk HPV infection. **(3)**

From a virological perspective, HPV is an epitheliotropic DNA oncovirus with over 120 subtypes identified. High-risk types like HPV-16 and HPV-18 are known to initiate a significant proportion of cervical and anogenital cancers, as well as OPSCC. The oncogenic potential of these HPV types is attributed to the E6 and E7 oncoproteins, which target the pRB and p53 tumor suppressor pathways, leading to cellular mutations and cancer development.**(4,5,6)**

Radiologically, HPV-positive OPSCC often presents with distinct features: smaller primary tumors, well-defined margins, and a higher incidence of cystic nodal metastases compared to HPV-negative tumors, which typically show poorly defined borders and solid nodal consistency. Goldenberg et al. conducted a comprehensive analysis of imaging features of HPV-positive OPSCC, revealing a correlation with cystic nodal metastases and primary cancers of the tonsil and base of the tongue. They distinguished between necrotic and cystic nodal metastases, indicating different pathophysiologic and imaging entities.**(7,8)**

Histologically, HPV-positive tumors frequently exhibit non-keratinizing or basaloid pathology, moderate to poor differentiation, and a higher N stage, while HPV-negative tumors are more likely to invade adjacent tissues**(5)**. Studies have shown that HPV-positive tumors are associated with a decreased prevalence of distant metastases and a different pattern of metastasis compared to HPV-negative tumors .The American Joint Committee on Cancer (AJCC) staging guideline now incorporates the prognostic implications of HPV status in OPSCC, highlighting its importance in treatment planning and eligibility for clinical trials.**(9)**

Despite advancements in imaging and histopathology, accurately predicting the HPV status of OPHSCC based solely on these features remains challenging. However, certain radiological and histopathological characteristics, such as a non-smoking history, distinct imaging patterns, and specific histological subtypes, may raise suspicion for HPV-mediated disease and prompt further investigation. The study aims to investigate these predictors comprehensively, focusing on radiological features such as tumor size, volume, extent, and nodal characteristics, and their association with HPV-mediated OPHSCC.

Understanding these associations is crucial for improving risk stratification, treatment strategies, and patient outcomes in resource-limited settings like India, where direct HPV testing may not be feasible. By elucidating these radiological markers, clinicians can better identify HPV-mediated carcinomas and optimize patient management in the context of HPV-associated head and neck cancers. This study's findings could act as an indirect guide for identifying HPV-mediated carcinoma, thereby contributing to enhanced treatment and quality of life for patients in resource-limited settings.

II. MATERIAL & METHODS:

This descriptive observational study was conducted from June 2022 to May 2024 with ethical approval and informed consent from all participants. It included 52 patients diagnosed with oropharyngeal and hypopharyngeal squamous cell carcinoma (OPHSCC). Patients underwent comprehensive evaluations, starting with a detailed history and physical examination to assess demographics, risk factors, and the extent of primary tumors and regional lymphadenopathy. Baseline hematological investigations included CBC, LFTs, RFTs, serum proteins, electrolytes, and coagulation profile. Radiological investigations involved CECT scans of the neck for all patients, MRI and PET-CT when indicated, to assess tumor size, location, volume, extent, lymph node metastasis characteristics (solid or cystic, margins), and extracapsular spread. Histopathological examinations included tissue sampling, standard H&E staining, and p16 immunohistochemistry to identify HPV-associated characteristics. Patients were planned for either neoadjuvant chemotherapy followed by radiotherapy or radical radiotherapy, based on tumor stage, performance status, and multidisciplinary discussions. Radiotherapy employed IMRT or 3DCRT techniques with conventional or hypofractionated schedules. Treatment planning and delivery were performed using Eclipse 15.6.06 and Varian LINAC DBX-600 linear accelerator, respectively. Statistical analysis, including Chi-square tests and unpaired t-tests, was conducted using Microsoft Excel and IBM SPSS Version 24 to examine associations between radiological and histopathological features and

high-risk HPV-mediated carcinomas, with significance determined at $p < 0.05$.

III. RESULTS & OBSERVATIONS

The study included 52 patients diagnosed with oropharyngeal and hypopharyngeal squamous cell carcinoma (OPHSCC). The population primarily comprised patients aged between 51-60 years, with a median age of 61 years. The mean age was 65 years for HPV-positive patients and 60 years for HPV-negative patients. Most participants were male (82.69%), with a smaller proportion of females (17.31%). Educational levels varied, with 46.15% having primary education, 34.62% being illiterate, 13.46% having secondary education, and 5.77% being graduates. Occupation-wise, nearly half were farmers (48.08%), followed by manual workers (32.69%), homemakers (11.54%), office workers (5.77%), and one business person (1.92%). A significant majority resided in rural areas (84.62%), with only 15.38% living in urban settings. Substance use was common, with 7.69% reporting no substance use, 3.85% using betel nut, 11.54% smoking tobacco, 15.38% using smokeless tobacco, 21.15% engaging in smoking tobacco, alcohol, and smokeless tobacco, 11.54% using both smoked and smokeless tobacco, and 28.85% using smoked tobacco and alcohol.

Table 1: Epidemiological Factors (N=52)

Factor	Category	Number of Patients (%)
Age	51-60 years	18 (34.6%)
	Median Age	61 years
	Mean Age (HPV+)	65 years
	Mean Age (HPV-)	60 years
Gender	Men	43 (82.69%)
	Women	9 (17.31%)
Education	Illiterate	18 (34.62%)
	Primary	24 (46.15%)
	Secondary	7 (13.46%)
	Graduate	3 (5.77%)
Occupation	Farmer	25 (48.08%)
	Manual Worker	17 (32.69%)
	Homemaker	6 (11.54%)
	Office Worker	3 (5.77%)
	Business	1 (1.92%)
Residence	Rural	44 (84.62%)
	Urban	8 (15.38%)
Substance Use	None	4 (7.69%)
	Betel Nut	2 (3.85%)
	Smoking Tobacco	6 (11.54%)
	Smokeless Tobacco	8 (15.38%)
	Smoking Tobacco, Alcohol and Smokeless Tobacco	11 (21.15%)
	Smoked Tobacco and Smokeless Tobacco	6 (11.54%)
	Smoked Tobacco and Alcohol	15 (28.85%)

Table2: Site Distribution of Patients (N=52)

Site	Number of Patients	Percentage
Hypopharynx	23	44.23%
Oropharynx	29	55.76%

The distribution of primary tumor locations among the participants reveals that the oropharynx is the most common site, accounting for 55.76% (29) of the cases, followed by the hypopharynx at 44.23% (23).

The stage group distribution among the participants indicates a predominance of advanced stages. Stage IVB is the most prevalent, representing 42.3% (22) of the cases, followed by stage IVA and stage III, each accounting for 21.2% (11). Early-stage

diagnoses are relatively uncommon, with stage I and stage II together making up 15.4% of the cases.

Table 3: Stage Group Distribution of Patients (N=52)

Stage Group	Frequency	Percentage
I	3	5.8%
II	5	9.6%
III	11	21.2%
IVA	11	21.2%
IVB	22	42.3%

Table 4: Stage Group Distribution of Patients (N=52)

HPV Status	Number of Patients	Percentage
HPV Positive	13	25%
HPV Negative	39	75%
Total	**52**	**100%**

Out of the 52 patients in the study, 13 were HPV positive (25%), while the remaining 39 were HPV negative (75%).

The histology grade distribution shows that moderately differentiated tumors (Grade II) are the most common, constituting 53.8% (28) of the cases. Poorly differentiated tumors (Grade III) follow at 32.7% (17), and well-differentiated tumors (Grade I) are the least frequent, making up 13.5% (7). Notably, none of the HPV-positive tumors were classified as Grade I, while 7 HPV-negative tumors fell into this category. Both HPV-positive and HPV-negative tumors predominantly fall into Grade II, with 7 and 21 cases respectively. Grade III tumors include 6 HPV-positive and 11 HPV-negative cases.

Table5: Histology Grade Distribution of Patients

Histology Grade	Frequency	Percentage	HPV+ (N=13)	HPV- (N=39)
I	7	13.5%	0	7 (17.94%)
II	28	53.8%	7 (53.84%)	21 (53.84%)
III	17	32.7%	6 (46.15%)	11 (28.20%)

In our study of 52 patients who underwent HPV testing, the analysis of radiological parameters revealed that nodal consistency and nodal margins are significantly associated with HPV status, highlighting their critical importance in understanding the radiological differences between HPV-positive and HPV-negative patients. Nodal consistency showed a significant variation ($p = 0.0402$), with HPV-positive patients more likely to have cystic nodes compared to HPV-negative patients. Similarly, nodal margins were significantly different between the two groups ($p = 0.0372$), with well-defined nodal margins more prevalent in HPV-positive patients (77%) than in HPV-negative patients (43.6%). Conversely, there were no significant differences in tumor volume ($p = 0.5352$) or nodal volume ($p = 0.4913$) between HPV-positive and HPV-negative patients.

Table 6: Radiological Parameters

Parameter	HPV Positive	HPV Negative	P-value	Significance
Nodal Margins			0.0372	Significant
Well-defined	10 (77%)	17 (43.6%)		
Ill-defined	3 (23%)	22 (56.4%)		
Nodal Consistency			0.0402	Significant
Solid	5 (38.46%)	29 (74.35%)		
Cystic	8 (61.53%)	10 (25.64%)		
Tumor Volume			0.5352	Not Significant
Mean (SD)	16.76 (23.15)	21.37 (21.73)		
Nodal Volume			0.4913	Not Significant
Mean (SD)	40.41 (94.30)	21.12 (48.17)		

IV. DISCUSSION

Human papillomavirus (HPV) has emerged as a significant etiological factor in the development of oropharyngeal and hypopharyngeal squamous cell carcinoma (OPHSCC). High-risk HPV strains, particularly HPV-16, are implicated in a distinct subset of these cancers, characterized by unique radiological and histopathological features. Recognizing these features is crucial for early diagnosis, appropriate therapeutic planning, and prognostication.

Given the rising incidence of HPV-mediated OPHSCC and different prognostic outcomes, it is imperative for HPV testing and understanding the interplay between radiological and histopathological characteristics, especially in Indian setups where resources may be limited. This study aims to investigate the role of radiological features as predictors of high-risk HPV-mediated OPHSCC, providing insights that may improve patient outcomes through tailored treatment strategies and better surveillance protocols.

The demographic data revealed the majority of patients were within the age range of 51-60, with a median age of 61 years. The mean age for patients with HPV-positive tumors was 65 years, while for HPV-negative tumors, it was 60 years. This distribution contrasts with several studiesfor instance, **Joseph and D'Souza (2012) (10)** highlighted that HPV-positive head and neck cancers are often diagnosed in younger populations, particularly those under 50 years of age. Similarly, **Elrefaey et al. (2014)(5)** noted that HPV-positive oropharyngeal cancer patients tend to be younger, with a median age of diagnosis at 54 years compared to their HPV-negative counterparts.

Gender distribution showed a significantly higher prevalence of HPV-mediated SCC in males (78.95%) compared to females (21.05%). This aligns with numerous studies reporting a higher incidence of HPV-related head and neck cancers in males due to higher exposure to risk factors and differences in sexual behavior and immune response.This gender disparity aligns with numerous studies that report a higher incidence of HPV-related head and neck cancers in males.Joseph and D'Souza (2012) found that males are disproportionately affected by HPV-positive head and neck cancers compared to females, with a male-to-female ratio of approximately 4:1. **Elrefaey et al. (2014) (5)** also reported a similar trend, emphasizing that the incidence of HPV-positive oropharyngeal cancer is significantly higher in males than in females

Regarding literacy, 46% of patients had primary education, 35% were illiterate, 14% had secondary education, and 5% were graduates. The occupation data revealed that 49.12% of patients were farmers, indicating a socio-economic dimension to the prevalence of HPV-mediated SCC. The majority of patients resided in rural areas (85.96%), suggesting an agrarian or suburban lifestyle, which is associated with limited access to healthcare and a higher prevalence of risk behaviors such as tobacco and alcohol use.This aligns with studies that link lower socio-economic status to higher incidences of head and neck cancers. For instance, a study conducted by **McDonald et al (2014)(11)** in Canada found that lower-income quintiles were significantly associated with poorer survival rates in head and neck cancer patients.

Substance abuse was prevalent among 93% of the patients, with smoked tobacco combined with alcohol being the most common form. This high prevalence of substance abuse is significant as both tobacco and alcohol are well-established risk factors for head and neck cancers. Studies by **Herrero et al. (2003) (12)** and **Hashibe et al. (2007)(13)** have extensively documented the interaction between tobacco, alcohol, and HPV in increasing the risk of oropharyngeal cancers.

The clinical characteristics showed a predominance of Stage IVB disease, often associated with poorer treatment outcomes. Histology grades reflected the heterogeneous nature of SCC, with varying degrees of cellular differentiation observed among patients. Poorly differentiated tumors were predominant, indicating an aggressive nature of the disease.These findings align with other studies that indicate a high prevalence of advanced-stage diagnoses in head and neck squamous cell carcinoma (HNSCC**). Barsouk et al. (2023)(14)** emphasized the significant proportion of patients presenting with advanced stages (Stage III and IV) of HNSCC, reflecting the aggressive nature of the diseaseThe distribution of staging in our study is comparable to those reported in other research. For example, a study by **Lechner et al. (2022) (2)** highlighted similar patterns of advanced stage presentations, with a high incidence of stage IV cases among HPV-positive patients

The distribution of cancer sites in our study, shows a balanced distribution between hypopharynx (HPX) and oropharynx (OPX), reveals that the oropharynx is the most common site, accounting for 55.76% (29) of the cases, followed by the hypopharynx at 44.23% (23).

Our study evaluated the radiological features of HNSCC, focusing on tumor volume, nodal volume, nodal margins, and nodal consistency. These parameters are essential for assessing disease extent and planning treatment.

Tumor Volume: The mean tumor volume was 16.76 cm^3 for HPV-positive patients and 21.37 cm^3 for HPV-negative patients ($p = 0.5352$), showing no significant difference. This is consistent with literature suggesting HPV-positive tumors typically have smaller volumes, correlating with better prognoses, as noted by **Adrian et al. (2022) (15)**

Nodal Volume: The mean nodal volume was higher for HPV-positive patients (40.41 cm^3) compared to HPV-negative patients (21.12 cm^3), with a p-value of 0.4913, indicating no significant difference. This aligns with findings that HPV-positive tumors often have higher nodal volumes due to extensive nodal disease caused by the virus.

Nodal Margins: There was a significant difference in nodal margins ($p = 0.0102$). HPV-positive patients had more well-defined nodal margins (11 cases) compared to ill-defined (2 cases), while HPV-negative patients had more ill-defined nodal margins (22 cases) than well-defined (17 cases). Well-defined margins, more common in HPV-positive tumors, are associated with better prognosis, as noted by **Huang et al.(8).**

Nodal Consistency: Significant variation was observed in nodal consistency ($p = 0.0402$). In HPV-positive patients, 8 cases were cystic and 5 solid, whereas in HPV-negative patients, 10 were cystic and 29 solid. Cystic nodal consistency, more common in HPV-positive patients, is associated with better clinical outcomes and is a distinguishing feature of HPV-associated cancers, as described by **Goldenberg et al. (2008)(16).**

Our findings align with existing studies, showing that HPV-positive tumors generally have smaller primary volumes, higher nodal volumes, well-defined margins, and cystic nodal consistency, linked to better outcomes. Conversely, HPV-negative tumors tend to be larger, with ill-defined and solid nodal metastases, indicative of a more aggressive disease course. These distinctions are crucial for tailoring treatment and improving patient outcomes.

V. CONCLUSION

This study highlights the significance of radiological features in differentiating between HPV-positive and HPV-negative oropharyngeal and hypopharyngeal squamous cell carcinoma (OPHSCC). Key findings from our analysis include:

1. **Nodal Consistency**: HPV-positive patients were significantly more likely to present with cystic nodes compared to HPV-negative patients ($p = 0.0402$). Cystic nodal consistency is a hallmark of HPV-positive cancers and is associated with better clinical outcomes.
2. **Nodal Margins**: HPV-positive patients exhibited a higher incidence of well-defined nodal margins compared to their HPV-negative counterparts ($p = 0.0102$), indicative of a better prognosis.
3. **Tumor and Nodal Volume**: Although the mean tumor volume was smaller for HPV-positive patients and the mean nodal volume was higher, these differences were not statistically significant. Nonetheless, the trend aligns with existing literature suggesting that HPV-positive tumors typically have smaller primary tumor volumes and larger nodal volumes.

These radiological characteristics are critical for early diagnosis, accurate staging, and tailored treatment strategies for OPHSCC. Our findings reinforce the distinct pathophysiological and prognostic profiles of HPV-positive and HPV-negative tumors, highlighting the importance of integrating radiological imaging in the diagnostic workflow for HPV-associated head and neck cancers.In resource-limited settings where direct HPV testing may not be feasible, identifying these radiological markers can serve as an indirect method for predicting HPV status, enhancing treatment planning and patient outcomes.

Overall, this study supports the role of radiological imaging in the evaluation and management of head and neck cancers, emphasizing the need for continued research and clinical application in this field.

VI. LIMITATIONS

This study faced several limitations. The smaller-than-expected sample size reduced statistical power. Conducted at a single institution, the results may not be generalizable to other regions with different epidemiological characteristics. Radiological assessments varied due to differences in imaging equipment and interpretation, and not all features were uniformly captured across patients. Additionally, limited follow-up data for some patients affected the comprehensiveness of the findings.

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