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Breakthrough in Human Papilloma Virus Screening and Molecular Comprehension in Head and Neck Malignancies: Ramifications for Clinical Care

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Abstract: Recent advancements in the detection of human papillomavirus (HPV) and the understanding of molecular mechanisms in head and neck cancers have revolutionized clinical management strategies. HPV has emerged as a critical factor in oropharyngeal squamous cell carcinoma (OPSCC), highlighting the urgent need for enhanced screening and diagnostic techniques. Innovative molecular approaches, such as next-generation sequencing and the identification of specific biomarkers, have significantly improved our ability to detect HPV-related lesions and to characterize tumor biology with greater precision. These advancements provide vital insights into patient prognosis, treatment efficacy, and potential therapeutic targets, paving the way for more effective and tailored interventions. Furthermore, a deeper understanding of the molecular pathways influenced by HPV allows for the development of personalized treatment strategies and preventive measures. This tailored approach not only enhances patient outcomes but also empowers clinicians to make more informed decisions. This review underscores the critical importance of integrating HPV detection and molecular profiling into standard care for patients with head and neck cancers. By doing so, patient management can be transformed, ultimately leading to better survival rates and quality of life for those affected by these devastating diseases. The future of oncology rests on leveraging these advanced technologies to guarantee that each patient receives the most suitable and effective treatment.

Key words: Human Papillomavirus, Oropharyngeal Carcinoma, HPV-Related Tumors, Biomarkers, Diagnosis and screening Methods, Treatment Strategies

I. Introduction

Head and neck cancer includes tumors originating from the oral cavity, oropharynx, larynx, hypopharynx, and sinonasal tract, representing a significant global health challenge and ranking as the sixth most common cancer worldwide.[1] These tumors share several characteristics, including a higher prevalence in males during their fifth and sixth decade of life, strong links to tobacco and alcohol use or betel nut chewing, and similar histopathological features.[2] Approximately 90% of head and neck cancers are classified as squamous cell carcinomas (HNSCC).[3] The estimated annual incidence of HNSCC is around 650,555 new cases, resulting in approximately 300,000 deaths, making it the sixth leading cause of cancer mortality.[4] OPSCC (**Figure 1**) accounts for roughly 50,000 cases, which is relatively low compared to other forms of HNSCC.[5]

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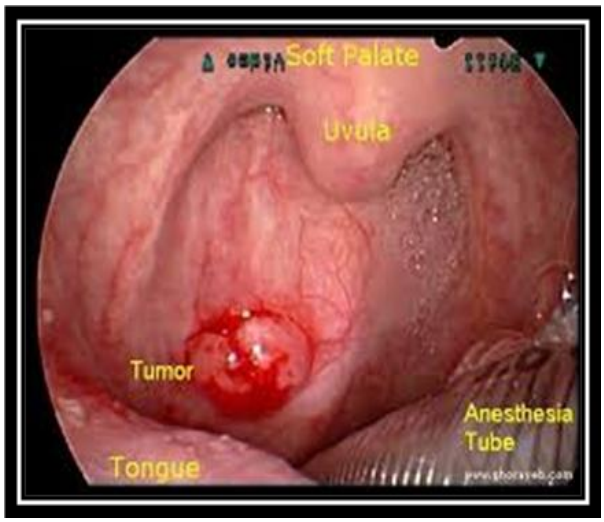

Figure 1: OPSCC
Courtesy:https://step2.medbullets.com/oncology/120411/oropharyngeal-cancer

Research indicates that the overall incidence of HNSCC has remained stable or even declined since the late 1980s, primarily due to decreasing rates of smoking and alcohol consumption, the main risk factors for these cancers.[6] However, the incidence of OPSCC, particularly in the base of the tongue and tonsil regions, has increased by 2-3% annually from 1973 to 2001, accelerating to 5.22% annually from 2000 to 2004 in several regions.[7]

Similar trends have been observed in various countries, with projections suggesting that HPV-associated oropharyngeal cancers may soon exceed the incidence of invasive cervical cancer.[8] Discrepancies in OPSCC incidence exist between developed and developing countries. In the developing world, OPSCC accounts for a low proportion of HNSCC, typically ranging from 1 to 10%, and this rate appears stable or even declining over time.[9] In contrast, developed countries show a higher and more variable proportion of OPSCC, generally between 15 and 30%.[10] For instance, some central European countries report OPSCC proportions as high as 30% among HNSCCs, while the overall incidence of HNSCC has remained stable or declined.[11] These demographic insights have prompted researchers to explore additional risk factors contributing to OPSCC incidence.[12] The recognition of HPV as a major etiological factor has transformed our understanding and management of head and neck cancers.[13] HPV is now acknowledged for its significant role, accounting for approximately 71% of OPSCC cases in various regions worldwide, with HPV-16 implicated in 85 to 96% of these instances.[14] This increase underscores the urgent need for a reevaluation of screening, diagnostic, and treatment protocols. Recent advancements in molecular biology, particularly through next-generation sequencing and the identification of specific biomarkers, have enhanced our ability to detect HPV-related lesions and understand their biological behavior. Distinguishing between HPV-positive and HPV-negative tumors is essential, as HPV-positive tumors generally demonstrate better treatment responses and improved prognoses, necessitating tailored therapeutic strategies.[15] This review examines the progress in HPV identification and molecular insights in head and neck tumors, emphasizing the significant implications these advancements have on treatment strategies. Integrating these developments into clinical practice aims to enhance patient outcomes and promote more personalized management of head and neck cancers.[16]

Discussion: HPV is recognized as a significant carcinogen, particularly associated with several malignancies, including cervical, oropharyngeal, anal, and other anogenital cancers.[17]

HPV Characteristics and Classification:

HPVs are non-enveloped viruses that pose significant health risks due to their ability to induce malignancy in epithelial tissues. Characterized by circular double-stranded DNA genomes, HPVs primarily target cutaneous and mucosal epithelia. The World Health Organization (WHO) recognizes 14 high-risk HPV types, with HPV-16 alone responsible for over 85% of HPV-positive OPSCCs.[18] At approximately 55 nm in diameter, these viruses lack an envelope and exhibit a strong affinity for epithelial cells. Their genomes, consisting of about 8,000 base pairs, are organized into three distinct regions: the early (E) segment, the late (L) segment, and the long control region (LCR). The E region comprises eight essential genes, while the L region contains two. The LCR, a critical non-coding regulatory area, is vital for initiating viral DNA replication and transcription.[19] To date, over 200 distinct genotypes of the papillomaviridae family have been identified, categorized into mucosal and cutaneous types based on their epithelial preferences.[20] These genotypes are further divided into high-risk and low-risk categories according to their potential to induce malignant transformations. High-risk types, including HPV-16, 18, 31, and 33, are associated with severe squamous intraepithelial lesions and invasive cancers, while low-risk types, such as HPV-6, 11, 40, and 42, are typically linked to benign lesions.[21] The oncogenic potential of HPV is primarily driven by the expression of the early proteins E6 and E7.[22] These

potent oncoproteins disrupt critical tumor suppressor pathways by inhibiting p53 and reyinoblastoma (Rb) proteins, facilitating uncontrolled cell proliferation.[23] E6's interactions with Postsynaptic Density Protein, Drosophila Zonal Protein (PDZ) domain-containing proteins further compromise cellular adhesion and polarity, while E7's engagement with cellular cyclins and kinases drives viral replication and cellular transformation, integral to HPV-associated tumorigenesis.[24] In addition to E6 and E7, other early genes—E5, E4, E1, and E2—play vital roles in the viral life cycle. E5 enhances cell growth and immune evasion, promoting viral replication.[25] E4 aids in viral particle assembly by disrupting the cellular cytoskeleton, while E1 is essential for initiating viral DNA replication, and E2 regulates viral gene expression and genome stability.[26] Collectively, these early genes embody the virus's multifaceted strategies for survival and malignancy, underscoring HPV's role as a formidable human carcinogen.[27] The complex interplay of HPV's genetic components and their impact on host cellular mechanisms reveals critical insights into the virus's contribution to cancer development, emphasizing the urgent need for continued research, prevention, and therapeutic strategies against HPV-related diseases.[28]

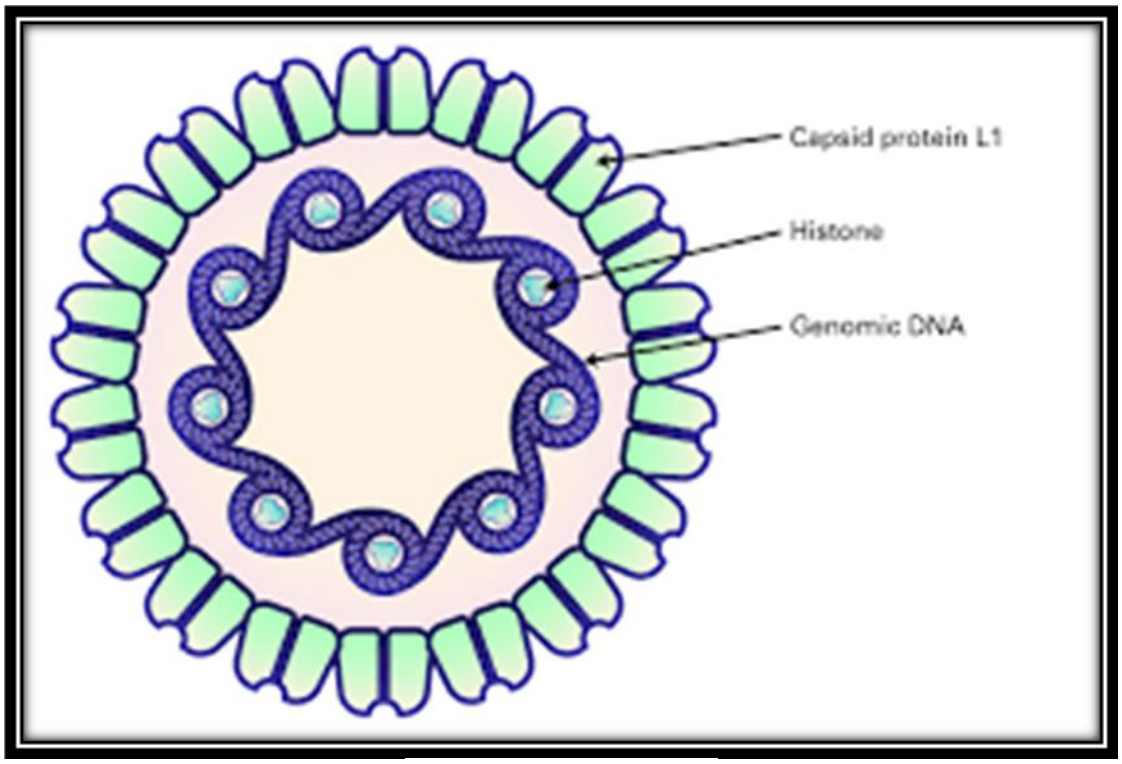

Figure 2: Structure of HPV
Courtesy: https://www.lsbio.com/research-areas/infectious-disease/papillomaviridae

Viral Life Cycle and Carcinogenic Potential:

The productive life cycle of HPV-16 relies on keratinocyte differentiation and is linked to persistent infection in immune-privileged sites like the tonsillar crypts. This transition from productive replication to malignant transformation involves changes in viral and host gene expression, particularly through the oncogenes E6 and E7, which promote cell-cycle entry and viral replication.[29] HPVs have circular double-stranded DNA, approximately 8000 base pairs long, with over 200 recognized types.[30] Among these, 14 mucosal HPV types are classified as high-risk by the WHO, including HPV-16, 18, 31, and 33.[31] Epidemiological and experimental evidence supports their association with cancer, notably in cervical cancer.[32] The relationship between HPV-16's life cycle and keratinocyte differentiation is critical in carcinogenesis, commonly occurring through persistent infection and immune-protected environments.[33] This process involves modifications in viral and host gene expression, significantly impacting the host genome. A key phase in HPV-induced carcinogenesis is marked by the activation of E6 and E7, which initiate the cell cycle in the epithelial basal layer and enable viral genome

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replication.[34] Heightened E6 and E7 expression is often linked to the integration of high-risk HPV DNA into the host genome, although carcinogenesis can occur without such integration.[35] Recent research emphasizes the interplay between HPV and cellular differentiation pathways.[36] The interruption of the E2 gene, which suppresses E6 and E7 during productive infection, is commonly seen in OPSCCs with integrated HPV and is associated with poor prognosis.[37] Clinical importance arises from the HPV genome's physical state in HPV-positive OPSCC patients; those with integrated HPV show shorter overall survival and reduced antitumor immunity.[38] E6 and E7 proteins of HPV play crucial roles in promoting cell-cycle entry and DNA replication while modifying the host genome, contributing significantly to cancer characteristics.[39]

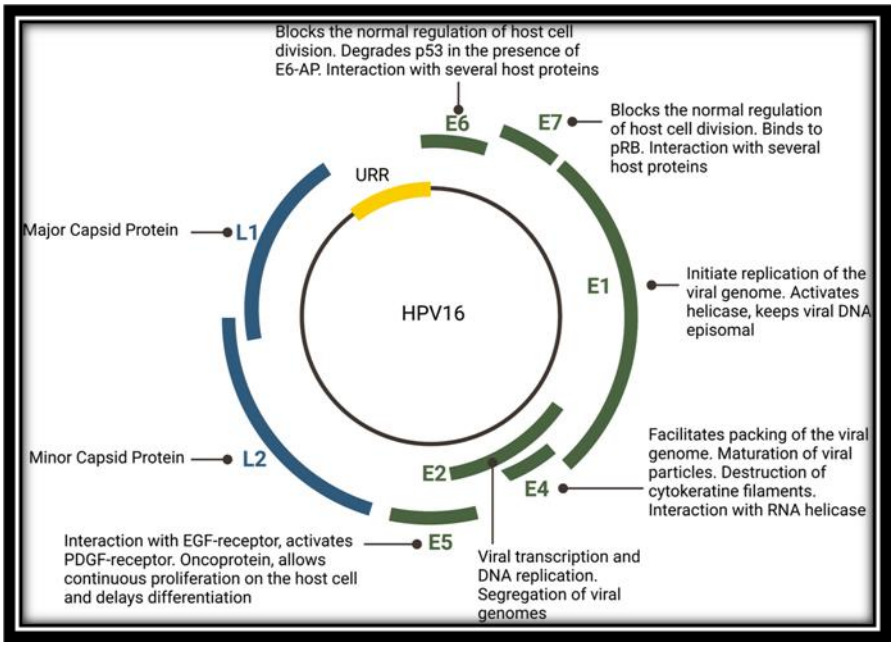

Figure 3: Oncogenic Roles of E6 and E7
Courtesy: Tran NH, Sais D, Tran N. Advances in human papillomavirus detection and molecular understanding in head and neck cancers: implications for clinical management. Cancer Epidemiol. 2024; 96(6):e29746.

Impact of Smoking on HPV-positive Tumors:
While TP53 mutations are infrequent in HPV-positive tumors, they can occur in heavy smokers, linking smoking to worse outcomes (**Figure 4**). This highlights the interplay between viral and host factors in cancer progression.[40]

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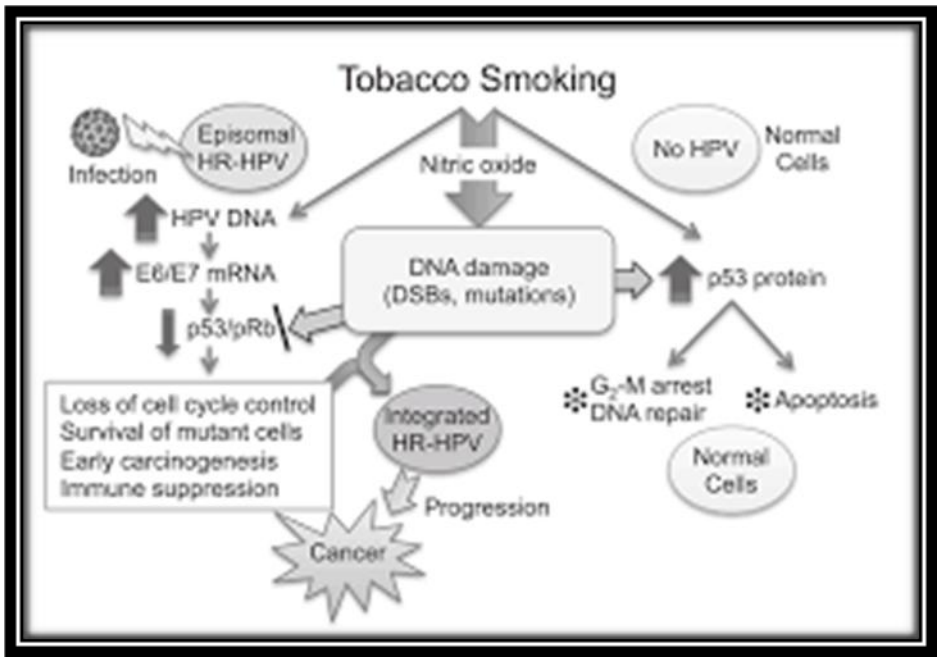

Figure 4: Smoking's role in HPV-positive tumor outcomes
Courtesy: Wei L, Anastac. Tobacco exposure results in increased E6 and E7 oncogene expression, DNA damage and mutation rates in cells maintaining episomal human papillomavirus 16 genomes. Carcinogenesis. 2014; 35(10):2373–81.

Role of APOBEC Enzymes:

Apolipoprotein B mRNA Editing Catalytic Polypeptide (APOBEC) enzymes typically suppress viral replication but may introduce mutations into the host genome, especially in HPV-positive OPSCC (**Figure 5**). This off-target activity can lead to oncogenic mutations in the Phosphatidylinositol 4, 5-bisphosphate 3-kinase catalytic subunit alpha." gene, a key component of the Phosphoinositide 3-kinase (PI3K) signaling pathway, associated with improved survival in HPV-positive OPSCC patients, particularly those using non-steroidal anti-inflammatory drugs (NSAIDs).[41]

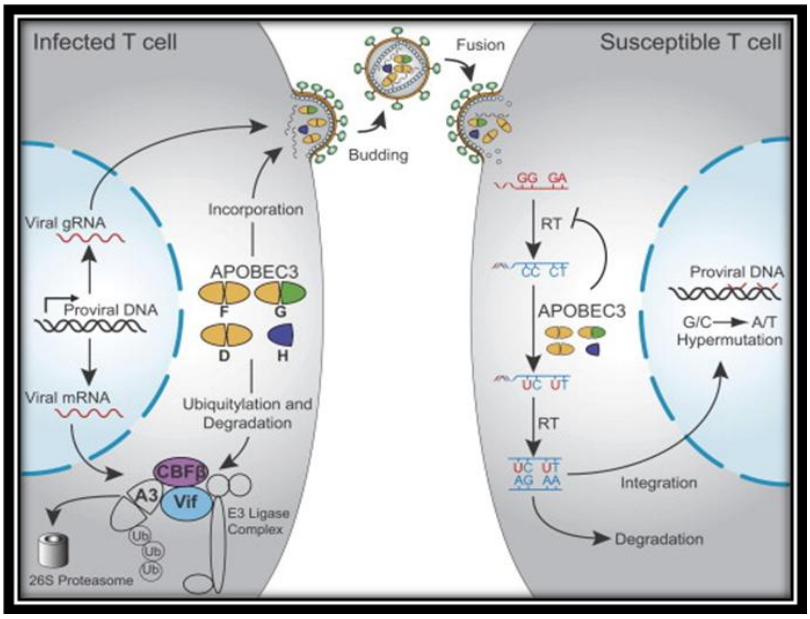

Figure 5: APOBEC Enzymes: Dual Role in HPV
Courtesy: Harris RS, Dudley JP. APOBECs and virus restriction. Virology. 2015; 479-480:131-45.

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Mechanisms of Malignant Transformation:

Extensive research has unveiled the critical role of HPV oncogenes E6 and E7 in malignant transformation, primarily through their targeted degradation of essential tumor suppressors' p53 and Rb (**Figure 6**).[42] This disruption dismantles crucial cell-cycle checkpoints, driving unchecked DNA replication and contributing to the hallmarks of cancer. E6 accelerates the degradation of p53, while E7 sabotages Rb function, leading to profound genomic instability and evasion of apoptosis.[43] E7's interference with Rb not only halts senescence-like responses but also activates Lysine (K)-Specific Demethylase KDM6B and KDM6A.[44] This activation triggers significant epigenetic reprogramming, altering chromatin states and DNA methylation patterns. Such changes upregulate homebox (HOX) genes and uniquely depend on the p16INK4A tumor suppressor—a departure from other cancers where CDK4/6 inhibitors are effective.[45] Notably, the expression of p21CIP1 through KDM6A is vital for managing DNA replication stress induced by E7.[46] A staggering 74% of HPV-positive OPSCC cases show high-risk HPV DNA integrated into the host genome, often correlating with poorer prognoses due to persistent E6 and E7 expression.[47] In contrast, HPV-negative OPSCCs frequently exhibit heightened mutation rates in the TP53 gene, which remains largely intact in HPV-positive tumors because of E6's action.[48]Moreover, HPV oncoproteins activate the PI3K/AKT/mTOR pathway, promoting enhanced cell survival and growth, while interference with the Notch signaling pathway disrupts cell differentiation and proliferation in HPV-positive OPSCCs.[49] Emerging evidence points to complex interactions with the Wnt/β-catenin pathway, further complicating the cancer landscape.[50] Overall, the intricate interplay of these pathways reveals the profound mechanisms underpinning HPV-induced oropharyngeal cancers, underscoring an urgent need for targeted therapeutic strategies. While challenges persist in directly targeting E6 and E7 due to their lack of enzymatic activity, a deeper understanding of their roles in epigenetic reprogramming and cell-cycle dysregulation opens promising avenues for innovative therapies.[51]

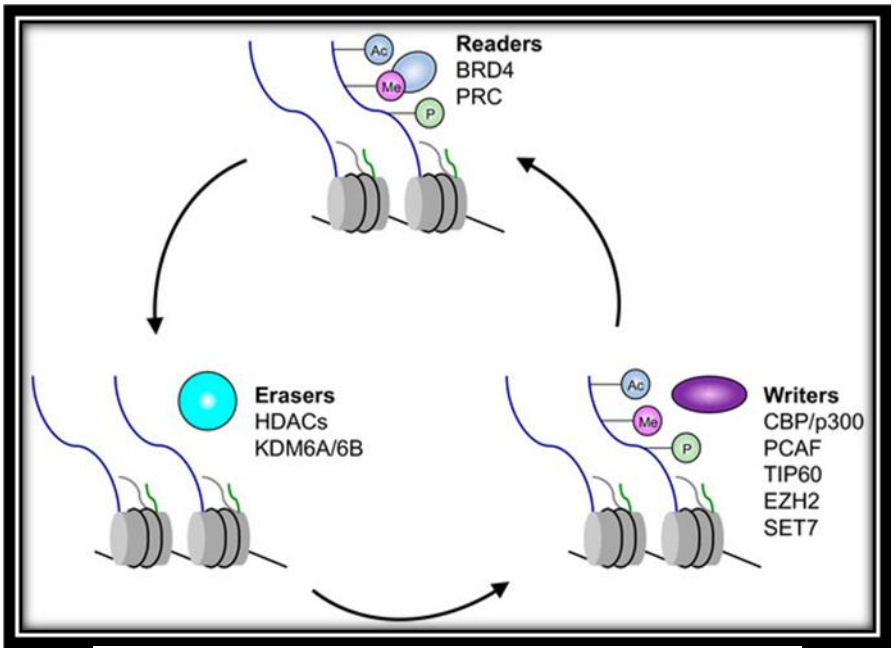

Figure 6: Mechanisms of Rb Function Inhibition in carcinoma
Courtesy: Verde G, Querol-Paños J, Cebrià-Costa JP, Pascual-Reguant L, Serra-Bardenys G, Iturbide A, Peiró S. Lysine-Specific Histone Demethylases Contribute to Cellular Differentiation and Carcinogenesis. Epigenomes. 2017; 1(4):4.

Genomic Characteristics of HPV-positive vs. HPV-negative OPSCC:

Somatic Alterations

HPV-positive OPSCCs display lower genomic instability than HPV-negative tumors, with fewer copy-number alterations, although the overall somatic variant load is comparable and the characteristics of these alterations differ significantly.[52] While the overall somatic variant load is comparable, the characteristics of these

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alterations differ considerably.[53] HPV-negative cases frequently harbor TP53 mutations due to tobacco exposure, while HPV-positive tumors often display mutations resulting from APOBEC3 activity.[54] Immune evasion in HPV-positive tumors includes downregulation of MHC class I molecules, impeding recognition by CD8+ T cells. The presence of HPV-specific T cells in the tumor microenvironment is a critical prognostic factor, with strong associations between T cell infiltration and overall survival. **Table 1** comparison of the genomic characteristics of HPV-positive versus HPV-negative OPSCC.[55]

Table 1: Genomic Traits of HPV-Positive vs. Negative OPSCC

Characteristic	HPV-Positive OPSCC	HPV-Negative OPSCC
Prevalence	**Increasing incidence, especially in younger, non-smoking populations**	**Historically more common, but decreasing in some areas due to tobacco control**
Key Mutations	**Typically fewer mutations overall; TP53 mutations are rare due to E6-mediated degradation**	**Higher mutation rates, especially in TP53, leading to genomic instability**
Tumor Suppressor Involvement	**Inactivation of p53 (via E6) and Rb (via E7); relies on p16INK4A**	**Frequently shows TP53 mutations and other genetic alterations affecting Rb and p16INK4A**
Genomic Stability	**Generally more stable due to lower mutation burden**	**Higher genomic instability, leading to more aggressive disease**
Epigenetic Changes	**Significant epigenetic reprogramming; activation of KDM6A and KDM6B**	**Less pronounced epigenetic alterations**
Molecular Pathways	**Activation of PI3K/AKT/mTOR pathway; involvement of Notch and Wnt pathways**	**Dysregulation of multiple pathways, often driven by smoking-related changes**
Prognosis	**Generally better prognosis and response to treatment**	**Often worse prognosis and more aggressive behavior**
Immune Response	**Enhanced immune response due to viral antigens**	**Typically lower immune response; often associated with chronic inflammation**

Diagnosis and Prognosis:

Patients with OPSCC often present with neck masses or oropharyngeal symptoms, complicating initial diagnosis due to similarities with benign conditions. Accurate assessment of HPV status is essential for guiding treatment choices and predicting outcome.[56] Current diagnostic protocols recommend a combination of immunohistochemistry for p16 and in situ hybridization for high-risk HPV DNA to ensure precise classification.[57] Current HPV detection methods have undergone significant advancements, leading to improved accuracy and efficiency.[58]

These methods encompass Nucleic Acid Amplification Tests (NAATs), including polymerase chain reaction (PCR) and digital PCR, recognized as the gold standard, with a focus on quantifying viral load.[59] Hybrid Capture Assays, next-generation sequencing, and the combination of Pap smear and HPV DNA testing for heightened sensitivity is prominent trends.[60] Additionally, immunohistochemistry identifies viral oncoproteins in tissue samples, while the development of point-of-care and saliva-based tests aims to increase accessibility.[61] Ongoing research explores novel biomarkers such as microRNAs and DNA methylation patterns for enhanced early detection. Quantitative PCR and HPV genotyping, achieved through multiplex PCR assays and DNA microarrays, continue to play a crucial role in assessing risks associated with HPV infection,

ultimately contributing to the prevention and early diagnosis of HPV-related cancers.[62]

AJCC Staging Guidelines:

Recent updates to the AJCC staging guidelines emphasize the importance of HPV status in prognostic differentiation, advocating for treatment de-escalation for HPV-positive patients, who typically have better outcomes. **Table 2** summarizes the key changes in the AJCC staging system for OPSCC, emphasizing the integration of HPV status and the reclassification of T and N stages.[63]

Table 2: AJCC Staging System for HPV-Positive OPSCC

Category	7th Edition Limitations	8th Edition Changes
Need for Change	**- HPV-positive patients generally have a better prognosis. - Up to 80% classified as stage IV despite early lymph node involvement. - Other classification systems (e.g., ICON-S) provided better survival estimates. - Lower 5-year overall survival in stage I–II than in III–IV. - N staging had limited impact on overall survival; only N2c showed worse survival.**	**- Integrates HPV status into staging criteria. - HPV positivity determined by p16 testing, requiring moderate to diffuse staining in ≥75% of tumor cells.**
T Staging	**- Tis (in situ) included. - T0 applies to all cases. - T4a and T4b categorized separately.**	**- Tis excluded for p16-positive cases. - T0 applies only to p16-positive metastatic lymph nodes. - T4a and T4b merged into a single T4.**
Clinical N Staging (p16-Positive)	**- Standard categories without specific criteria for HPV status.**	**- N1: Ipsilateral nodes ≤6 cm. - N2: Bilateral/contralateral nodes ≤6 cm (no subcategories). - N3: Nodes >6 cm.**
Clinical N Staging (p16-Negative)	**- Standard categories without changes.**	**- N3 divided into: - N3a: Nodes >6 cm without extranodal extension. - N3b: Signs of extranodal extension.**
Pathological N Staging	**- Remains unchanged for p16-negative OPSCC. - Specific definitions for p16-positive staging lacking.**	**- For p16-Positive OPSCC: - N1: ≤4 metastatic lymph nodes (laterality ignored). - N2: >4 metastatic nodes. - N3 removed. - For p16-Negative OPSCC: Remains unchanged from the 7th edition.**

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The transition from the 7th to the 8th edition of the UICC/AJCC TNM staging system for OPSCC marks a pivotal shift, largely driven by the inclusion of HPV status. [64] Implemented in January 2018, the 8th edition defines HPV positivity through p16 testing; establishing clear classification criteria.[65] Key changes include the exclusion of Tis in p16-positive OPSCC and a redefined T0 category, alongside the unification of T4a and T4b into a single T4 category.[66] Clinical N staging was also updated: N1 now encompasses ipsilateral lymph nodes ≤6 cm, while N2 includes bilateral or contralateral nodes ≤6 cm. For p16-negative OPSCC, N3 was subdivided into N3a (nodes >6 cm without extranodal extension) and N3b (with extranodal extension).[67]

Validation of the 8th edition of the AJCC staging system for OPSCC:

Validation studies confirm that the 8th edition significantly enhances the ability to discriminate between stages.[68] Research by Park et al. revealed a notable shift in staging, with over 85% of HPV-positive patients classified as stages III and IV under the 7th edition, reduced to 76.1% in stages I and II under the 8th edition.[69] Similarly, Sharma et al. reported an increase in stage I and II patients from 7.9% to 62.9%.[70] These findings highlight the profound impact of the 8th edition on staging and survival outcomes, underscoring its role in improving prognostic stratification for patients with HPV-positive OPSCC. This evolution in the staging system not only refines clinical management but also enhances our understanding of the disease's biology and prognosis.[71]

Risk Stratification

The Radiotherapy Oncology Group (RTOG) has categorized patients into low, intermediate, and high-risk groups based on HPV status, tobacco use, and lymph node involvement. [72]

Treatment options and monitoring

Treatment for OPSCC may involve surgical excision, primary radiotherapy, or chemoradiotherapy.[73] Advances in surgical techniques have shifted focus to minimally invasive approaches like transoral laser microsurgery (TLMS) and transoral robotic surgery (TORS) (**Figure 7**) for early-stage cases.[74]

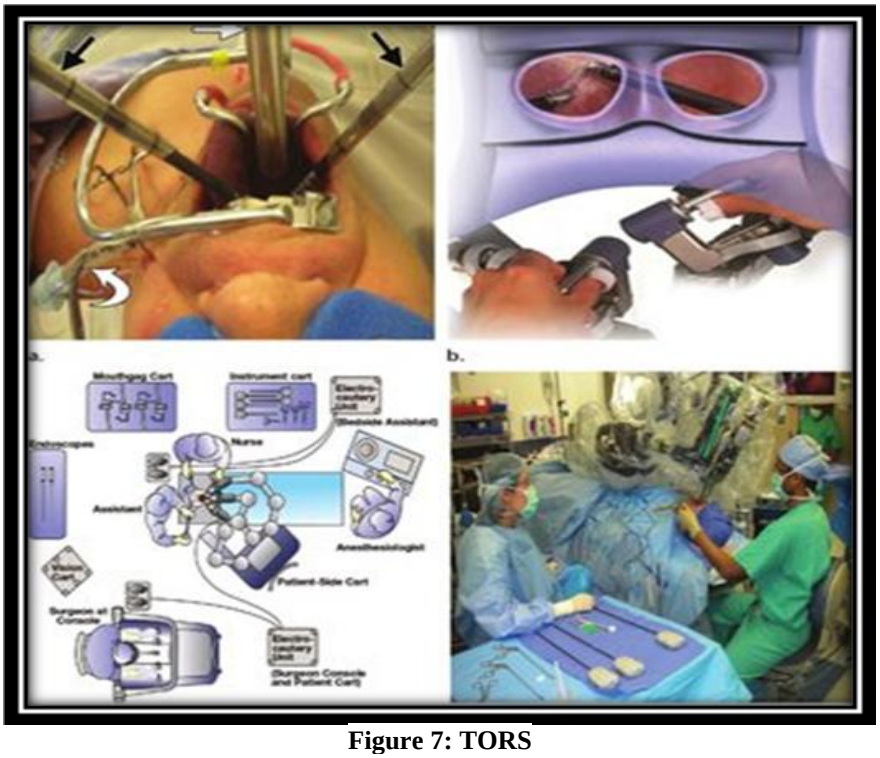

Figure 7: TORS

Courtesy: Loevner L, Learned KO, Mohan S, O'Malley BW, Scanlon MH, Rassekh CH, Weinstein GS. Transoral robotic surgery in head and neck cancer: what radiologists need to know about the cutting edge. Radiographics. 2013; 33(6):1759-1779.

Adjuvant treatments: Primary radiotherapy and chemo radiotherapy remain standard, typically delivering 66–70 Gy with concurrent platinum-based chemotherapy. Although HPV-positive OPSCC generally has a favourable prognosis, 10–25% of patients may experience disease recurrence, primarily within the first two years post-diagnosis.[75]

Monitoring protocols: Regular clinical assessments and monitoring of HPV DNA as a biomarker for tracking post-treatment disease status are crucial.[76] Persistent detection of HPV DNA in oral rinses and plasma samples has been effective for identifying recurrences.[77] Ongoing trials are investigating the feasibility of reduced-dose adjuvant radiotherapy for high-risk patients and exploring de-intensification strategies for low-risk cases, with the goal of optimizing treatment while minimizing side effects.[78] While adjuvant therapy effectively lowers local and regional recurrence rates, it has not significantly enhanced overall survival due to high salvage rates.[79] Patients treated with TORS alone report better quality of life and functional outcomes, likely due to the avoidance of adverse effects linked to adjuvant therapy, such as dry mouth and painful swallowing.[80] When adjuvant radiotherapy is warranted, reducing the radiation dose for patients with favourable risk factors like negative surgical margins can help lessen treatment-related complications while maintaining effectiveness.[81] Studies indicate that lowering adjuvant radiation from 60–66 Gy to 30–36 Gy in such patients leads to improved swallowing and overall quality of life, while still achieving excellent control rates.[82] Current studies, including PATHOS and ECOG3311, are evaluating the safety and efficacy of de-intensified adjuvant therapy following TORS.[83] Preliminary findings suggest that primary TORS with reduced postoperative radiotherapy, without chemotherapy, produces excellent oncological outcomes alongside favourable quality of life measures in patients with intermediate-risk HPV-positive OPSCC.[84]Further research, such as the Systemic Inflammatory Response Syndrome (SIRS) and Minimally Invasive Neck Dissection (MINT) trials, will continue to refine treatment strategies based on pathological characteristics, focusing on optimizing adjuvant therapy for both low and high-risk patients.[85]

Outcomes with primary chemoradiotherapy: Despite the encouraging outcomes associated with minimally invasive surgical techniques, primary radiotherapy and chemo radiotherapy continue to be prevalent treatment options for OPSCC.[86] Over the last decade, initiatives to reduce radiation doses have demonstrated excellent oncological results and decreased morbidity rates.[87] Research shows high pathological response rates with reduced-dose intensity-modulated radiotherapy (IMRT) (**Figure 8**) combined with low-dose cisplatin for early-stage disease, achieving 3-year local and regional control rates along with an overall survival rate of 95%.[88]

Figure 8: IMRT
Courtesy: https://www.topdoctors.co.uk/medical-dictionary/intensity-modulated-radiation-therapy-imrt

For advanced-stage patients (stages III–IV), induction chemotherapy followed by reduced-dose chemo radiotherapy has become a viable strategy. This approach seems to diminish the risk of treatment-related complications while maintaining acceptable survival rates. Patients who respond favourably to induction chemotherapy often have radiosensitive tumors, potentially improving both oncological outcomes and long-term functional status, including swallowing and overall quality of life.[89]

Chemotherapy necessity: Research indicates that radiotherapy alone may be sufficient for patients with locally advanced HPV-positive disease.[90] In contrast, radiotherapy alone is less effective for p16-negative or HPV DNA-negative OPSCC, though there are no significant differences in survival outcomes for patients with p16-positive and HPV DNA-positive cancers.[91] The extent of disease also plays a critical role in determining the need for concurrent chemotherapy.[92] A retrospective analysis revealed that concurrent chemo radiotherapy reduced the risk of metastatic disease in high-risk HPV-positive OPSCC patients but not in low-risk cases.[93] Conversely, a phase II trial suggested that adding cisplatin improved disease-free survival in low-risk HPV-positive patients compared to those receiving radiotherapy alone.[94] Thus, reliable conclusions about the safety and efficacy of excluding chemotherapy from treatment cannot yet be drawn.[95] Ongoing and future clinical trials are crucial for assessing treatment de-escalation in well-

defined settings.[96] Trials like EVADER and HYHOPE are investigating survival outcomes with reduced-dose radiotherapy with or without chemotherapy, while the quarterback trials are focused on advanced-stage disease.[97] A retrospective analysis of the National Cancer Database found no statistically significant differences in overall survival between patients receiving primary TORS and those undergoing primary radiotherapy. This suggests that both treatment modalities may offer comparable outcomes for patients, highlighting the need for further investigation into the nuances of surgical approaches in head and neck cancer management.[98]While survival outcomes appear similar, the differing toxicity profiles and potential morbidities should guide clinical decision-making.[99] The ORATOR trial was the first to investigate outcomes between TORS and primary chemo radiotherapy, but its modest sample size limited definitive conclusions. Similar quality outcomes were noted, along with varying treatment-specific toxicities. Ongoing studies like ORATOR2 aim to provide further insights into overall survival outcomes in larger cohorts. **Table 3** outlines UK/US treatment recommendations for HPV-positive OPSCC management.[100]

Targeted Therapies:

Table 3: UK/US Treatment Recommendations for HPV-Positive OPSCC

Approach	Early stage (T1 or T2 N0)	Late stage (T3 or T4 N0; T1–4 N1–3)
Open Surgery	**- Not typically recommended; prefer Transoral robotic surgery/ Transoral laser microdissection or definitive Radiotherapy**	**- Usually, Paramedian mandibulotomy or Trans-cervical pharyngotomy for tongue base resections. - G/LR not frequently used; mandibulectomy for gross bony involvement. - Lip-splitting mandibulotomy required for adequate visualization. Reconstruction using radial artery free or anterolateral thigh free flaps. - Also used for surgical salvage. - Adjuvant Chemoradiotherapy or Post-operative radiotherapy usually required. - Modified or selective neck dissection recommended.**
Transoral Surgery	**- Transoral robotic surgery/ Transoral laser microdissection for T1/T2; potentially T3. - Ipsilateral selective neck dissection recommended; N0 treated electively. - Adjuvant radiotherapy/ Chemoradiotherapy based on tumor features.**	**- Limited to early-stage disease.**
Definitive radiotherapy	**- Radical radiotherapy (70 Gy/35 fractions) or hypofractionated radiotherapy (65–66 Gy/30 fractions).**	**- Usually restricted to patients with no prior head and neck irradiation or substantial comorbidities.**

	- Intensity-modulated radiotherapy. - Prophylactic radiotherapy to ipsilateral nodes for lateralized tumors; both sides for non-lateralized tumors.	**- Cetuximab may be safer for patients with pre-existing conditions. - Investigated in trials for de-escalation.**
Definitive chemoradiotherapy	**- 70 Gy radiotherapy (2 Gy fractions) with concurrent cisplatin (100 mg/m² on days 1, 22, and 43 or 40 mg/m² weekly).**	**- Restricted to patients for whom surgery is not indicated or preferred to avoid surgery. - Technical feasibility influenced by extratonsillar disease involvement.**
Adjuvant Therapy	**- Chemoradiotherapy (70 Gy radiotherapy with concurrent cisplatin) for positive or close margins or extranodal extension; improves outcomes for extracapsular invasion/microscopically involved margins.**	**- Post-operative radiotherapy (70 Gy RT) can be with or without concurrent chemotherapy. - Not recommended for those >70 years old or with poor performance status.**

Several clinical trials are investigating targeted therapies alongside traditional treatments. Cetuximab, an anti-EGFR monoclonal antibody, has been evaluated as a replacement for cisplatin to reduce treatment-related toxicities.[101] However, although cetuximab has a comparable adverse event profile, it has demonstrated inferior locoregional disease control and higher rates of distant metastases.[102] Notably, genomic studies have identified differences in EGFR expression between HPV-positive and HPV-negative tumors. One promising strategy involves combining reduced chemotherapy with ribavirin and the EGFR/HER2 inhibitor afatinib, which has shown safety in patients with locally advanced HPV-positive OPSCC.[103]This approach aims to leverage the oncogenic dysregulation caused by the HPV E6 protein. Immunotherapy represents a promising frontier in the treatment of HPV-positive malignancies.[104] The anti-programmed cell death protein 1 (anti-PD-1)antibodies nivolumab and pembrolizumab have shown potential, with trials indicating better outcomes for HPV-positive patients.[105] However, systematic reviews reveal mixed results regarding the link between HPV status and treatment response.[104] Ongoing trials, including the use of the anti-programmed cell death ligand 1 (anti-PD-L1) antibody atezolizumab in the adjuvant setting, aim to clarify these relationships.[106] Neoadjuvant studies combining nivolumab with stereotactic body radiation therapy (SBRT) have shown high pathological complete response rates in HPV-positive groups.[107]

Further research is essential to disentangle the contributions of each modality.[108] The combination of durvalumab and SBRT is also being investigated. Therapeutic vaccines targeting HPV E6 and E7 antigens have been explored, with some trials reporting encouraging outcomes when used in conjunction with immune checkpoint inhibitors. Several ongoing studies aim to establish the safety and efficacy of these vaccines combined with immunotherapies.[109] As the treatment landscape for OPSCC evolves, ongoing and future trials will be crucial in shaping standard care. Understanding the interplay between treatment modalities, HPV status, and patient-specific factors will help clinicians optimize therapeutic strategies for better outcomes in HPV-positive OPSCC patients.[110]

Future Directions: Ongoing research emphasizes the need to integrate molecular insights into standard care for HPV-related cancers, especially OPSCC.[111] Key objectives include identifying safe methods to de-escalate chemo radiation, as most primary tumors respond well to current treatments. A major challenge is pinpointing the 15-20% of high-risk tumors that may recur and developing effective therapies for recurrent cases. Recent studies indicate that recurrent HPV+ OPSCCs may share mutations, like TP53, with HPV– cancers, influencing treatment strategies.[112] Variations in viral gene expression between good- and poor-prognosis tumors also suggest potential for targeted therapies. Additionally, mutations in PRKDC found in metastatic lesions point to the use of PARP inhibitors, such as olaparib. However, further

research with larger patient cohorts is needed to confirm these findings.[113]

Key areas for future research include:

1. **Enhanced screening techniques:** Improving HPV detection methods, such as liquid biopsies and advanced imaging, to enable earlier diagnosis.
2. **Personalized treatment protocols:** Developing targeted therapies based on molecular mechanisms of HPV-positive tumors to improve efficacy and reduce toxicity.
3. **Longitudinal studies:** Assessing long-term outcomes of HPV-positive vs. HPV-negative tumors to inform treatment guidelines.
4. **HPV vaccination awareness:** Increasing global access to vaccination programs to reduce the incidence of HPV-related cancers, especially in underserved populations.
5. **Multi-omics approaches:** Utilizing integrated data from various biological layers to discover novel biomarkers for diagnosis and prognosis.
6. **Addressing disparities:** Focusing on education, screening, and vaccination initiatives to tackle disparities in HPV-related cancer incidence.
7. **Collaboration and data sharing**: Encouraging partnerships among researchers, clinicians, and institutions to enhance understanding and accelerate the discovery of new therapeutic targets.

By pursuing these strategies, there is potential to significantly improve diagnostic accuracy, treatment effectiveness, and overall patient outcomes in HPV-related head and neck cancers.[114]

II. Conclusion

Recent advancements in recognizing HPV and molecular analyses have transformed the understanding of head and neck tumors, especially OPSCC. HPV's role as a key etiological factor reshapes clinical management, emphasizing targeted screening and personalized treatment. Differentiating between HPV-positive and HPV-negative tumors is crucial, as HPV-positive cases generally show better treatment responses. Integrating molecular profiling into clinical practice enhances diagnostic accuracy and informs treatment decisions, improving patient outcomes. The fight against HPV-related cancers necessitates urgent action for more effective interventions. Ongoing research underscores the need to incorporate these insights into standard care. A comprehensive strategy involving HPV screening, vaccination, and personalized treatment is essential for effectively addressing head and neck cancers and improving survival rates and quality of life. Leveraging the growing understanding of HPV is vital for revolutionizing treatment and enhancing cancer care outcomes.

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