https://doi.org/10.31925/farmacia.2026.4.4 **REVIEW**

VIRAL INVOLVEMENT IN ONCOGENESIS OF OROPHARYNGEAL SQUAMOUS CELL CARCINOMA: FROM MOLECULAR MECHANISMS TO THERAPEUTIC STRATEGIES

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Abstract

Cancer is the second leading cause of global mortality, with approximately 20% of cases attributable to infectious agents. Among the seven recognised oncogenic viruses, high-risk human papillomavirus (HPV) has driven an epidemic-like rise in oropharyngeal squamous cell carcinoma (OPSCC) across industrialised nations, even as tobacco-related disease declines. This narrative review provides an integrated, mechanistically grounded synthesis of viral involvement in oropharyngeal carcinogenesis. We discuss the molecular basis of transformation, E6- and E7-mediated inactivation of p53 and Rb within the crypt epithelium of Waldeyer's ring, through the disease's distinctive epidemiology, including the pronounced European gradient and the Romanian context, to its diagnosis, p16-based biomarker classification, and the divergent AJCC 8th edition staging. Particular emphasis is placed on therapeutic management: stage-based standards, the cautionary failure of cetuximab substitution, the rationale for de-escalation, and the emergence of immunotherapy in the curative setting. We conclude by highlighting the principal unmet needs that will shape future practice.

Rezumat

Cancerul reprezintă a doua cauză de mortalitate la nivel mondial, aproximativ 20% dintre cazuri fiind atribuite agenților infecțioși. Dintre cele șapte virusuri oncogene recunoscute, tulpinile cu risc înalt ale papilomavirusului uman (HPV) au determinat o creștere de proporții, de tip epidemic, a carcinomului scuamos orofaringian (OPSCC) în țările industrializate, în paralel cu declinul patologiei asociate consumului de tutun. În acest studiu este discutată implicarea virală în carcinogeneza orofaringiană. Sunt prezentate bazele moleculare ale transformării maligne, inactivarea proteinelor p53 și Rb prin intermediul oncoproteinelor E6 și E7 la nivelul epiteliului criptic al inelului Waldeyer, apoi este discutată epidemiologia specifică a patologiei, precum prevalența europeană ridicată și contextul românesc. Un accent deosebit este pus pe managementul terapeutic: standardele stabilite în funcție de stadiu, eșecul relevant al înlocuirii cu cetuximab, argumentele în favoarea dezescaladării terapeutice și apariția imunoterapiei în context curativ. În final, sunt evidențiate principalele nevoi încă nesatisfăcute care vor contura practica medicală viitoare.

Keywords: Human papillomavirus, oropharyngeal squamous cell carcinoma, treatment de-escalation, cancer pharmacotherapy, immunotherapy

Introduction

Cancer remains one of the foremost challenges to global health, standing as the second leading cause of mortality worldwide and accounting for nearly one in six deaths (1). While carcinogenesis is classically conceived as a stepwise accumulation of somatic mutations driven by intrinsic errors and environmental exposures, a substantial and often under-appreciated proportion of the global cancer burden is infectious in origin (2). According to estimates from the WHO and its specialised cancer agency, the International Agency for Research on Cancer (IARC), approximately 20% of all human cancers are attributable to infectious agents, bacteria, parasites, and, most prominently, viruses (3). While this review focuses on directly oncogenic viruses, the infection-attributable fraction also includes major non-viral contributors, most notably the bacterium *Helicobacter pylori*, the single largest infectious cause of cancer worldwide, and carcinogenic parasites such as *Schistosoma haematobium* and the liver flukes *Opisthorchis* and *Clonorchis* (4).

This recognition reframes a meaningful share of oncology as, in principle, preventable, since the inciting agent can often be vaccinated against, screened for, or treated.

Among infectious causes, a defined group of seven viruses (Figure 1) is directly oncogenic, driving transformation through their own gene products, each linked to characteristic malignancies through distinct molecular routes (IARC additionally classifies HIV-1 as carcinogenic to humans, though it acts indirectly, through immunosuppression rather than direct transformation, and is therefore considered separately here as a cofactor).

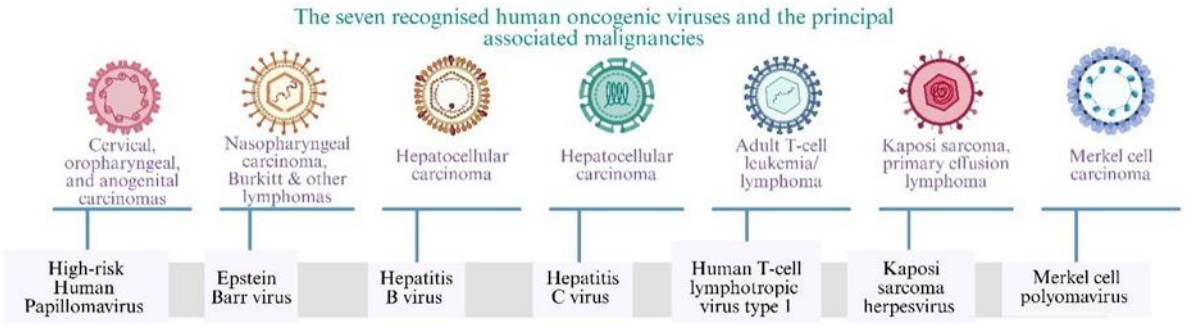

Figure 1.
The seven recognised human oncogenic viruses (Created with BioRender.com)

Within this group, HPV has acquired singular public health importance in the context of head and neck cancer. Over recent decades, the incidence of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) has risen to epidemic-like proportions across industrialised nations, even as tobacco-related disease has declined, so much so that HPV now accounts for the majority of oropharyngeal cancers in many high-income countries (5). Unlike its tobacco-driven counterpart, this is a disease of younger, often otherwise healthy individuals, with a distinct biology, a markedly more favourable prognosis, and, critically, the prospect of prevention through vaccination (6). These features make it both a clinical opportunity and an unresolved public health challenge, particularly given the absence of any validated screening method.

The conceptual foundations of viral oncology were laid incrementally over more than a century. Early experimental hints emerged with Ciuffo, who in 1907 demonstrated the transmissibility of human warts through cell-free filtrates, implicating a viral agent. Decades later, Shope's identification of the cottontail rabbit papillomavirus (1933), and its subsequent malignant progression demonstrated by Rous and Kidd, established a firm link between papillomaviruses and proliferative, and ultimately neoplastic, epithelial disease in animal models (7). The decisive conceptual leap came with Harald zur Hausen, whose work, culminating in the early 1980s, notably the identification of specific HPV types in cervical cancer around 1983, established high-risk HPV as a genuine human carcinogen and ultimately earned a Nobel Prize. The extension of this paradigm to the head and neck followed, with investigators such as Brandsma and Abramson providing early evidence of HPV involvement in oropharyngeal tumours, presaging the epidemic now unfolding (8).

Against this background, the present narrative review aims to provide an integrated, mechanistically grounded synthesis of viral involvement in oropharyngeal carcinogenesis, tracing the path from the molecular mechanisms by which HPV transforms the tonsillar epithelium, through the disease's distinctive epidemiology, diagnosis and staging, to current therapeutic strategies, and the unmet needs that will define future practice.

Viral Oncogenesis

Malignant transformation fundamentally constitutes a malfunction of the genome's two principal regulatory categories: proto-oncogenes, which promote proliferation, and tumour suppressor genes, which inhibit it. Proto-oncogenes such as *MYC*, *RAS*, or *CCND1* behave like cellular accelerators; a single gain-of-function event, point mutation, amplification, or aberrant activation is sufficient to convert them into dominant oncogenes. Tumour suppressors such as *TP53* and *RB1*, by contrast, act as inhibitory mechanisms, and their loss is classically recessive at the cellular level, typically requiring biallelic inactivation as Knudson's two-hit model predicts (9). Carcinogenesis requires simultaneous inhibition of accelerators and removal of inhibitors. Oncogenic viruses are remarkable precisely because they can accomplish both, supplying compact genetic toolkits that hijack these pathways far more efficiently than the slow accumulation of somatic mutations (10).

Nevertheless, association alone is insufficient to consider a virus genuinely oncogenic. Epidemiological consistency must be reinforced by mechanistic criteria: the viral genome (or its transforming genes) should be present in tumour cells but absent or markedly reduced in surrounding normal tissue; expression of

viral oncoproteins should be demonstrable and necessary for the transformed phenotype; and experimental silencing of these genes should reverse malignancy (11, 12). The convergence of these requirements explains why only seven human viruses, HPV, EBV, HBV, HCV, HTLV-1, KSHV and Merkel cell polyomavirus, are confidently classified as directly carcinogenic, despite the vast number of human-infecting viruses (13).

Beyond these formal criteria, oncogenic viruses share a recurring biological pattern. First, they establish persistent infection, since transformation is a multistep process unfolding over years or decades; transient, rapidly cleared infections rarely transform (14). Secondly, and in a comparable manner, they must refrain from destroying the host cell, as a deceased cell cannot develop into a tumour. This restriction encourages the use of non-cytolytic strategies, latency, episomal maintenance, or restrained gene expression, which maintain the infected cell's viability while gradually disrupting its growth control (15). HPV effectively demonstrates this by tying its life cycle to epithelial differentiation, rather than lysing the basal cells on which it relies (16).

Therefore, viral infection is rarely sufficient on its own. The overwhelming majority of individuals infected with these agents never develop cancer, which underscores that oncogenic viruses are better understood as powerful initiators that require cofactors to complete transformation. Two cofactor categories dominate. Immunosuppression, whether iatrogenic, as in transplant recipients, or acquired, as in HIV infection, removes the immune surveillance that normally eliminates virus-bearing cells, dramatically amplifying the incidence of EBV- and KSHV-driven malignancies (10, 17). The second determinant is chronic inflammation, which is characterised by a mutagenic, pro-survival microenvironment that is sustained by cytokine signalling, reactive oxygen species, and continuous reparative proliferation. This dynamic is vividly illustrated by HBV/HCV-associated hepatocellular carcinoma (18).

Molecular Mechanisms of HPV Oncogenesis

Genome architecture and the differentiation-linked life cycle

Human papillomaviruses are small, non-enveloped viruses carrying a circular, double-stranded DNA genome of roughly 8 kilobases. Despite this, the genome is functionally tripartite. The early (E) region encodes the non-structural proteins E1, E2, E4, E5, E6 and E7, which govern viral replication, transcriptional control, and, critically, host-cell reprogramming (19). The late (L) region encodes the two capsid proteins: L1 (the major capsid protein, which self-assembles into the immunogenic virus-like particles used in vaccines) and L2 (the minor capsid protein) (20). Interposed between them lies the long control region (LCR), a non-coding segment that contains the origin of replication together with the binding sites for E1, E2, and a constellation of host transcription factors. The LCR functions as the genome's regulatory control system, determining the timing and location of early promoter activation (21).

The defining feature of the HPV life cycle is its tight coupling to epithelial differentiation. The virus can establish infection only by reaching the basal layer of a stratified squamous epithelium, the sole compartment that retains proliferative, long-lived cells. Access typically requires a micro-wound that exposes basal keratinocytes. Once inside, the genome is established as a low-copy episome (around 50 - 100 copies *per* cell), maintained in the nucleus and partitioned to daughter cells with the help of E2, which tethers viral DNA to host mitotic chromosomes. In these basal cells, viral gene expression is deliberately restrained, a stealth strategy that preserves the reservoir (22).

As infected daughter cells leave the basal layer and migrate upward, the program changes. Normally, suprabasal keratinocytes exit the cell cycle and differentiate terminally. HPV subverts this: in the mid-to-upper epithelial strata, E6 and E7 expression rises, forcing differentiating keratinocytes to re-enter S-phase and thereby sustaining the DNA-replication machinery the virus needs to amplify its genome to thousands of copies (23). Only in the most superficial, terminally differentiated layers are the late genes L1 and L2 switched on, capsids assembled, and progeny virions shed within desquamating squames. This differentiation-dependent cascade explains why the productive life cycle is non-lytic and largely invisible to immune surveillance: replication and antigen-rich capsid production are physically confined to cells already destined to die and slough off (16).

In productive infection, E6 and E7 remain modulated by E2, which represses the early promoter. The main event in oncogenesis is frequently the integration of viral DNA into the host genome. Integration commonly disrupts the E2 open reading frame, abolishing E2-mediated repression and unleashing constitutive, deregulated overexpression of E6 and E7 (24). Integration also stabilises the viral-host fusion transcripts, prolonging their half-life. The result is a self-reinforcing loop: cells with the highest E6/E7 output gain a proliferative and survival advantage and are clonally selected. Importantly, integration is common but not obligatory; some HPV-driven tumours retain episomal or mixed forms, yet the functional endpoint, loss of E2 control over the two oncogenes, is a near-universal theme (24, 25) (Figure 2).

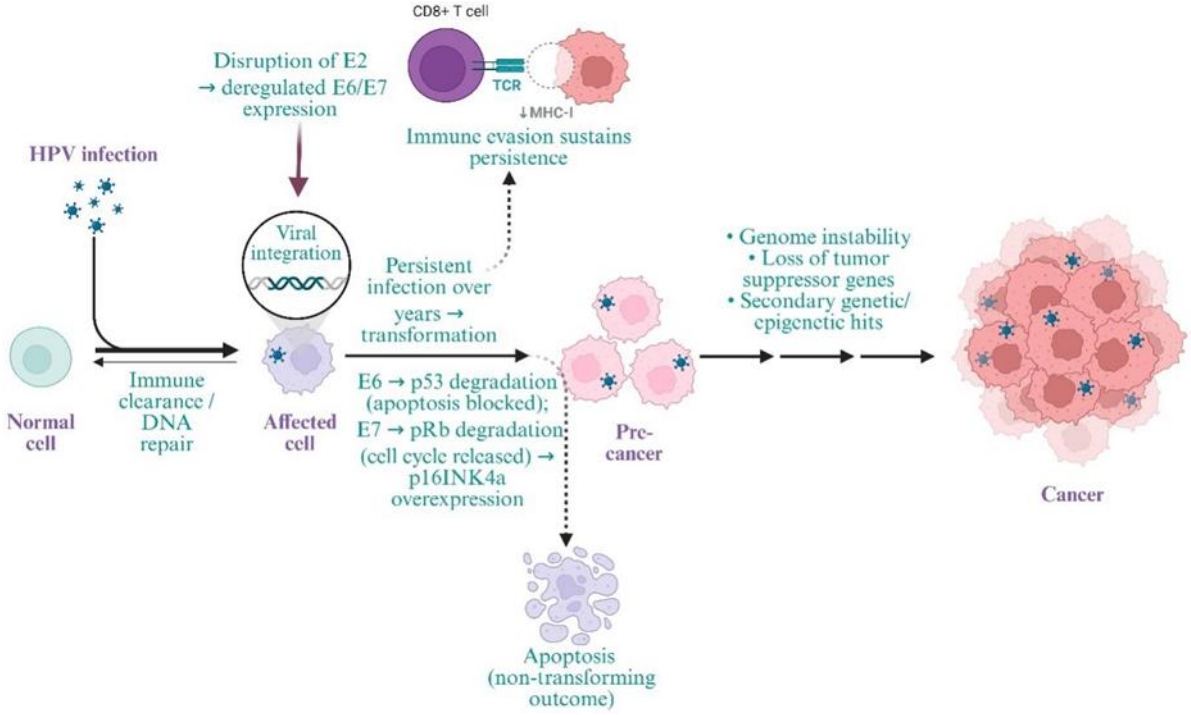

Figure 2.

Mechanism of HPV-driven carcinogenesis. Following HPV infection of a normal epithelial cell, most infections resolve: the cell either clears the virus through cell-mediated immunity or repairs the associated DNA damage, reverting to normal (leftward arrow). In a persistently infected minority, viral integration into the host genome disrupts the E2 open reading frame, abolishing E2-mediated repression and driving deregulated overexpression of the E6 and E7 oncoproteins. E6 targets p53 for degradation, disabling apoptosis, while E7 promotes pRb degradation, releasing the cell cycle and causing the reactive overexpression of p16INK4a that underlies its diagnostic use. Sustained oncoprotein expression over years, together with immune evasion (downregulation of MHC class I, impairing CD8+ T-cell recognition), permits the infected clone to persist and accumulate genome instability, loss of tumour-suppressor function, and secondary genetic and epigenetic hits, progressing through a precancerous stage to invasive carcinoma. Apoptosis of the affected cell (downward dashed arrow) represents a non-transforming outcome. (Created with BioRender.com)

The predilection of HPV for the oropharynx, and specifically the palatine and lingual tonsils (base of tongue), is anatomically determined. The tonsillar surface is deeply invaginated by crypts lined by a discontinuous, reticulated specialised epithelium. Unlike the smooth, multilayered keratinised epithelium covering most of the upper aerodigestive tract, the crypt epithelium is thin, non-keratinised, and structurally interrupted by infiltrating lymphocytes (26). This architecture brings the proliferative basal layer unusually close to the luminal surface, granting the virus comparatively easy access to its obligatory target cells without the need for a deep wound.

Two further features make the crypt an ideal viral reservoir. First, its discontinuous basement membrane and constant immune-cell trafficking create a permissive interface for viral entry. Second, the deep, sheltered crypt microenvironment is relatively sequestered from immune effector mechanisms and from mechanical clearance, allowing persistence (27). The crypt, thus, functions simultaneously as the portal of entry, the sanctuary for latency, and the eventual site of malignant transformation, explaining why HPV-positive oropharyngeal carcinomas characteristically arise from the depths of tonsillar tissue rather than the mucosal surface (28).

The E6/E7 oncoproteins and p16INK4a

E6 is one of the two master effectors of transformation, and its central function is the functional elimination of p53, the "guardian of the genome". In contrast to the somatic TP53 mutations that deactivate the gene in the majority of HPV-negative head and neck cancers, HPV-positive tumours generally maintain wild-type p53, yet effectively neutralise its function (29). High-risk E6 recruits a cellular E3 ubiquitin ligase, E6-associated protein (E6AP, encoded by *UBE3A*), forming an E6–E6AP complex that binds p53 and targets it for proteasomal degradation. Therefore, with p53 levels suppressed, the cell loses its capacity for cell-cycle arrest (*via* p21) in response to DNA damage and, equally, its capacity for apoptosis (30).

E6's pro-survival reach extends beyond p53. It upregulates the catalytic subunit of telomerase (hTERT)

through the E6-E6AP complex, both by relieving transcriptional repression of the hTERT promoter (in part by directing E6AP-mediated ubiquitination and degradation of the repressor NFX1-91) and by interacting with the telomerase complex directly, thereby conferring replicative immortality by preventing telomere erosion. It also interferes with pro-apoptotic effectors, degrading or inhibiting molecules such as BAK and disrupting death receptor signalling. It engages PDZ-domain proteins (including the scaffolding and polarity regulators DLG and Scribble) through its C-terminal PDZ-binding motif. This high-risk trait disrupts cell polarity and adhesion. The overall consequence of E6 is a cell that is unable to undergo apoptosis when necessary: DNA damage accumulates uncontrollably, and the apoptotic safeguard is eliminated (31, 32).

In simple terms, E7 forces proliferation. Its principal target is the retinoblastoma protein (pRb). In a normal cell, hypophosphorylated pRb sequesters the E2F family of transcription factors, holding the cell at the G1/S checkpoint. E7 binds pRb and promotes its degradation, liberating E2F and driving constitutive transcription of S-phase genes, DNA polymerases, cyclins E and A, and other replication machinery. The keratinocyte is thereby pushed into continuous cycling even in suprabasal layers where it should have withdrawn from the cell cycle (33, 34).

A molecular consequence of pRb destruction is the de-repression of the *CDKN2A* locus, which encodes p16INK4a. Typically, p16INK4a restrains the cell cycle by inhibiting CDK4/6, and its transcription is held in check by the intact pRb pathway. When E7 degrades pRb, this repression is lifted, driving marked overexpression of p16INK4a. Crucially, this accumulated p16INK4a is functionally impotent: its downstream target, pRb, has already been eliminated, so the block it would normally impose on CDK4/6 cannot be transmitted, and proliferation continues unchecked (35). This phenomenon is the molecular basis for the diagnostic use of p16. E7 additionally binds and functionally antagonises the CDK inhibitors p21 and p27, and induces genomic instability by dysregulating centrosome duplication, seeding the aneuploidy characteristic of these tumours (36).

The two oncoproteins are therefore complementary and synergistic: E7 drives unscheduled proliferation that would normally trigger p53-dependent apoptosis, while E6 simultaneously abolishes that apoptotic response. Neither alone is efficiently transforming; together, they immortalise human keratinocytes (37).

The strong, diffuse overexpression of p16INK4a that follows E7-mediated pRb loss provides a convenient, inexpensive immunohistochemical surrogate for transcriptionally active high-risk HPV infection. In the oropharynx, where the prior probability of HPV involvement is high, block-positive p16 staining, defined conventionally as strong nuclear and cytoplasmic positivity in at least 70% of tumour cells, correlates well with HPV status and with favourable prognosis, and it is incorporated into routine staging (38, 39).

Its limitations, however, demand interpretive caution, as p16 reports the consequence of pRb inactivation, not the virus itself, and pRb can be lost through HPV-independent mechanisms. Consequently, false positivity occurs: a subset of p16-positive tumours harbour no detectable transcriptionally active HPV, and these "p16+/HPV–" discordant cases do not share the excellent prognosis of truly HPV-driven disease (40, 41). This discordance is more frequent outside the oropharynx, where p16 performs poorly as an HPV marker and should not be used in isolation. The pragmatic conclusion is that p16 is an excellent screening surrogate within the oropharynx but, for definitive classification, particularly in equivocal or non-oropharyngeal sites, should be confirmed with a direct test of viral activity such as HPV E6/E7 mRNA detection or high-risk HPV DNA *in situ* hybridisation (42, 43).

Latency, Clearance, Persistence, Progression and Immune Evasion

The clinical behaviour of oral HPV mirrors its molecular biology and unfolds along several possible trajectories. The great majority of infections are transient and cleared within one to two years by an eventually mounted cell-mediated immune response; these never progress (44, 45). A second possibility is latency, in which the genome persists at very low copy number in basal cells with minimal gene expression, capable of reactivation if immune control later wanes, a reservoir that explains recurrences and infections in the absence of recent exposure (46).

The trajectory is the persistence of a transcriptionally active high-risk infection. It is the duration of persistence, more than infection *per se*, that drives risk: years of sustained E6/E7 expression provide the time and the genomic instability needed to accumulate the secondary genetic and epigenetic hits, frequently consolidated by viral integration and loss of E2 control, that complete malignant transformation (24, 47). Progression is, therefore, typically slow, with a long subclinical interval between exposure and the development of clinically apparent carcinoma. This protracted latency is biologically significant in two ways: it underlies the demographic profile of HPV-positive oropharyngeal cancer, which typically presents decades after presumed acquisition, and it defines, in principle, a wide window for intervention, though the absence of an accessible precancerous lesion in the tonsillar crypt currently leaves that window difficult to exploit (48).

Long-term persistence is unattainable without active immune evasion, which HPV does through a comprehensive strategy. The life cycle is immunologically

inert: there is no viremia, no cytolysis, and the most immunogenic proteins (the capsid antigens L1 and L2) are synthesised exclusively in the outermost, dying cells, furthest from immune surveillance (49). In addition to its passive stealth mechanisms, HPV plays an active role in suppressing local immune responses. The oncoproteins suppress type I interferon signalling; E6 and E7 interfere with interferon-regulatory factors and the JAK/STAT axis, blunting the antiviral response. They also downregulate antigen-presentation machinery, including MHC class I and the TAP transporter, reducing the visibility of infected cells to cytotoxic T cells (50).

A distinctive feature of the epithelium is the targeting of Langerhans cells, the resident dendritic-cell sentinels of the squamous mucosa. HPV-infected keratinocytes fail to deliver the danger signals and chemokines needed to recruit and activate these cells, and they suppress E-cadherin–mediated retention, producing a state of local immune ignorance rather than tolerance breakdown (51). The minor capsid protein L2 adds an additional degree of complexity: although L2 contains broadly cross-neutralising epitopes (a characteristic utilised in the development of next-generation vaccines), during natural infection, these epitopes remain largely concealed within the assembled virion, becoming briefly exposed only during cell entry. Consequently, the most cross-protective target is not readily recognised by the humoral immune system (52). Together, these mechanisms allow infected clones to go undetected for the prolonged interval required for transformation.

Anatomical Landmarks in HPV-Associated Cancers

The oropharynx is the middle division of the pharynx, situated between the nasopharynx above and the hypopharynx below. It extends superiorly from the plane of the soft palate to the level of the hyoid bone (or the vallecula) inferiorly, and it opens anteriorly into the oral cavity at the palatoglossal arch, the ridge formed by the anterior tonsillar pillar (53). Within these limits, four subsites are recognised: the base of the tongue (the posterior third, behind the circumvallate papillae), the palatine tonsils and tonsillar fossae, the soft palate with the uvula, and the posterior pharyngeal wall. Crucially, the two subsites that dominate HPV-positive disease are the palatine tonsils and the base of the tongue, and this is no coincidence: both are sites of dense lymphoid tissue (54).

The tonsillar fossa itself deserves particular attention because its surface is not smooth. Each palatine tonsil sits in a recess bounded by the palatoglossal (anterior) and palatopharyngeal (posterior) arches, and its epithelial surface is deeply invaginated by tonsillar crypts, branching, blind-ended channels that vastly amplify the surface area of contact between the external environment and the underlying lymphoid follicles (55). As discussed before, the crypts are lined by a thin, discontinuous, non-keratinised reticulated epithelium infiltrated by lymphocytes, an arrangement that brings the proliferative basal layer, the obligatory target of HPV, unusually close to the lumen. The crypt is thus the anatomical key to this cancer: portal of viral entry, sheltered reservoir for persistence, and ultimately the site of malignant origin, which explains why these tumours frequently arise deep within tonsillar tissue rather than on the visible mucosal surface and may present as an occult primary with a cystic neck node (56, 57).

This lymphoid tissue is not isolated but forms part of an integrated structure: Waldeyer's ring, the circumferential collar of mucosa-associated lymphoid tissue (MALT) guarding the entrance to the aerodigestive tract. The ring comprises the pharyngeal tonsil (adenoids) superiorly, the paired tubal tonsils around the Eustachian openings, the paired palatine tonsils laterally, and the lingual tonsil at the base of the tongue inferiorly. Functionally, Waldeyer's ring is a first line of immune defence, sampling inhaled and ingested antigens and initiating mucosal immune responses (58). Yet this same immunological specialisation is double-edged. The crypt epithelium is intrinsically a site of heavy, tolerized immune traffic, conditions that favour local immune evasion rather than viral elimination, allowing HPV to persist within the very tissue designed to surveil it.

In short, the oropharynx is anatomically predisposed to HPV oncogenesis: its tumour-prone subsites are precisely those endowed with crypt-bearing lymphoid tissue, where epithelial vulnerability and immunological permissiveness converge.

Epidemiological Profile and Risk Factors

The epidemiology of oropharyngeal squamous cell carcinoma (OPSCC) over the past three decades is best understood as the superposition of two divergent trends. The classical, HPV-negative disease, driven by tobacco and alcohol, has steadily declined in most industrialised nations, tracking the long-term fall in smoking prevalence (59). At the same time, the incidence of HPV-positive disease has increased so dramatically that, in high-income countries, it has not only reversed the decline but has also turned the overall trend of oropharyngeal cancer into a net increase. The population-level incidence of HPV-positive oropharyngeal cancers increased by roughly 225% from 1988 to 2004 in the United States, and HPV is now estimated to cause approximately 70% of oropharyngeal cancers in the US and other developed countries (60). The clinical entity has been so transformed that “oropharyngeal cancer” today denotes, in much of the West, a predominantly viral disease.

However, HPV-positive OPSCC is rising at the same time as HPV-driven cervical cancer is falling in countries with mature female vaccination programs. These opposite trajectories are not contradictory but reflect a generational and immunological lag: cervical cancer responds quickly to vaccination because effective screening exists and the target population was vaccinated first and most completely, whereas oropharyngeal cancer, lacking any screening, affecting predominantly men who were historically under-vaccinated, and arising decades after viral acquisition, will only begin to decline once vaccinated cohorts age into the at-risk window (5). The oropharyngeal epidemic is, in effect, the delayed shadow of an exposure pattern that herd immunity has not yet reached.

Moreover, the proportion of oropharyngeal tumours found to harbour HPV has climbed dramatically over time, a trend documented in archived tumour tissue. Globally, the HPV-attributable fraction of OPSCC rose from approximately 7.2% in the 1990 - 1994 period to the much higher contemporary figures (61). European single-institution series capture the same temporal shift: an Italian cancer-institute cohort, for instance, documented a significant increase in HPV-associated cases over time, from 40.3% in 2010 - 2014 to 53.7% in 2015 - 2019 (62). Importantly, the demographic of the "typical" patient has also broadened over this interval, with an increase in median age and a growing number of diagnoses in women, so that the disease is no longer confined to the young white men who defined its early epidemic phase.

However, HPV DNA positivity alone overstates the truly virus-driven fraction, because incidental, transcriptionally inactive DNA can be detected in tumours not actually caused by the virus. The rigorous definition of an HPV-driven tumour therefore requires evidence of viral activity, E6/E7 mRNA expression, or DNA positivity combined with p16 overexpression, rather than DNA detection in isolation (63).

Importantly, Europe does not behave as a uniform bloc. There is a pronounced geographic gradient, with the highest HPV-attributable fractions in Northern and Central Europe and substantially lower fractions toward the South and East. Pooled analysis of multinational trial cohorts established this gradient as an independent determinant of risk, finding that HPV-positive oropharyngeal cancer differed markedly between Western and Eastern Europe (37% *versus* 6%), a difference that persisted after accounting for tumour site and smoking (64). More recent national studies confirm high Southern-European fractions where rigorous methodology is applied: the Greek ORPHEAS study reported an HPV-mediated fraction of 52.1% in oropharyngeal cancer, of which 96% were attributable to 9-valent vaccine types, especially HPV16 (65).

Romania occupies a particularly instructive position within this gradient, and its data carry a cautionary lesson about the DNA-*versus*-driven distinction. In a Northeastern Romanian cohort analysed with a strict combined algorithm, 23 of 189 head and neck cases (12.2%) were HPV DNA-positive, including half of the oropharyngeal cases (14/28, 50.0%), a DNA prevalence in the oropharynx comparable to Western Europe (66). Yet when transcriptional activity was required, the picture collapsed: only two of 189 cases (1.1%) were genuinely HPV-driven, positive for both viral DNA and RNA. This discordance, high DNA prevalence but very low driven fraction, suggests that in this region, much detected HPV DNA may represent clinically irrelevant infection rather than true viral oncogenesis, and it underscores why p16 or mRNA confirmation is indispensable before attributing causation. As elsewhere, HPV16 was overwhelmingly the dominant type (86.9% of positive cases).

The Romanian context is further shaped by a competing risk-factor environment that favours the classical HPV-negative pathway. Romania carries one of the highest alcohol consumption rates in Europe and, despite falling tobacco use, one of the EU's highest cancer mortality rates, while neighbouring Hungary reports the EU's highest incidence of oral and oropharyngeal cancer in males (67). In such a setting, tobacco- and alcohol-driven disease remains proportionally larger, and the Western viral takeover of oropharyngeal cancer is less complete. Nonetheless, the prognostic biology still holds locally: a Western-Romanian series confirmed that p16-positive patients had significantly better survival and reported markedly lower alcohol and tobacco use than their p16-negative counterparts, validating the clinical relevance of the distinction even where the driven fraction is modest (68).

At present, the patient who tests positive for HPV tends to be younger, often by ten years or more, predominantly male, and comes from a higher socioeconomic and educational background. This individual is typically a never- or light-smoker with minimal or no history of alcohol consumption. Additionally, they report engaging in sexual-behavioural risk factors, identified as the primary means of acquiring oral HPV (69). The tumours arise preferentially in the crypt-bearing lymphoid subsites, the palatine tonsils and base of tongue, and characteristically present with small primaries but early cystic cervical nodal metastases, frequently as a neck mass with an occult primary. Across European series, these patients are consistently younger, more frequently have tonsillar tumours, and present less often at the highest TNM stage (70).

The HPV-negative patient, by contrast, is typically older, with a heavy tobacco and alcohol history, frequently presents with a larger, locally destructive primary tumour and field cancerization of the surrounding mucosa, and, critically, carries a substantially worse prognosis (71). The molecular correlate of this divide

(wild-type p53 functionally inactivated by E6 in HPV-positive disease *versus* mutated *TP53* in HPV-negative disease) underlies not only the differing biology but the divergent treatment responsiveness (72).

Diagnosis and Staging

Diagnosis begins with histological confirmation of squamous cell carcinoma. Still, the decisive step in the oropharynx is determination of HPV status, because it dictates staging, prognosis, and eligibility for de-escalation trials (73). The pragmatic first-line test is p16INK4a immunohistochemistry, the inexpensive surrogate for transcriptionally active high-risk HPV discussed in the molecular section. Positivity is defined by the conventional threshold of strong, diffuse nuclear and cytoplasmic staining in ≥ 70% of tumour cells ("block positivity") (74). Within the oropharynx, where pre-test probability is high, p16 alone is sufficient for routine classification and AJCC staging. As the European guidelines emphasise, however, the prognostic value of p16 is confined to oropharyngeal tumours; at other head and neck sites, it performs poorly and is not mandatory (75).

Because p16 reports the consequence of Rb loss rather than the virus itself, false-positive results occur, and confirmation is advisable in equivocal cases. Confirmatory tests, of increasing specificity, include high-risk HPV DNA *in situ* hybridisation and, as the gold standard for true viral activity, E6/E7 mRNA detection (76, 77). The proliferation marker Ki-67 serves as a useful adjunct: HPV-driven tumours show a high proliferative index, and combined p16/Ki-67 co-expression (analogous to cervical cytology dual-staining) increases confidence that p16 reflects genuine viral transformation rather than a non-specific reaction (78).

Cross-sectional imaging (contrast-enhanced CT or MRI of the primary and neck, often supplemented by PET-CT for nodal and distant staging) defines anatomic extent. For mucosal visualisation, Narrow Band Imaging offers a meaningful advantage over conventional white-light endoscopy: by filtering illumination to wavelengths absorbed by haemoglobin, NBI accentuates the aberrant superficial neovascular patterns of early neoplasia, improving detection of small or occult primaries, a frequent challenge in HPV-positive disease, where a tiny crypt-based primary may hide beneath a bulky cystic node (79,80).

The most consequential change in recent staging is that the AJCC 8th edition created an entirely separate staging system for p16-positive oropharyngeal cancer. The rationale was prognostic accuracy: under the old unified system, HPV-positive patients with extensive nodal disease were classed as advanced yet did remarkably well, distorting stage-based prognosis. The new system down-stages nodal burden, producing a dramatic stage migration in which patients formerly labelled stage IV now occupy stages I - II (81) (Table I).

Table I

Staging contrasts in AJCC 8th-edition oropharyngeal cancer by p16 status

Feature	p16-positive (HPV-driven)	p16-negative
Staging system	Separate, HPV-specific; two distinct schemes, clinical (cTNM) and pathological (pTNM)	Conventional (single scheme)
T category	T4a/T4b merged into a single T4; Tis category removed	T4a/T4b retained; Tis retained
Clinical N (cN) basis	Node size and laterality only: ipsilateral ≤ 6 cm = N1; bilateral/contralateral ≤ 6 cm = N2; any node > 6 cm = N3	Size, number, laterality, and extranodal extension
Pathological N (pN) basis	Node count: 1 - 4 nodes = N1; ≥ 5 nodes = N2 (applies only to surgically treated patients)	Same principles as clinical, refined by pathology
Extranodal (extracapsular) extension	Not incorporated into staging (no prognostic weight in this system)	Strongly upstaging (→ N3b)
Bilateral/contralateral nodes ≤ 6 cm	N2 (with T1–T2, → stage II)	Stage IVB
Stage IV threshold	Reached only with M1 (distant metastasis)	Reached far earlier
Prognostic implication	Markedly favourable	Substantially worse

The clinical takeaway is that identical anatomic disease yields a much lower stage and a much better predicted outcome when p16-positive, which is precisely why accurate HPV testing is a necessity in the entire diagnostic procedure. However, a distinctive feature of the p16-positive system is its division into two separate nodal schemes: clinical (cN), based on node size and laterality, and pathological (pN), based on the number of involved nodes (1 - 4 = N1; ≥ 5 = N2). The pN scheme applies only to surgically treated patients, since nodal status cannot be reliably assessed preoperatively. Extranodal extension, strongly upstaging in p16-negative disease, carries no staging weight in the p16-positive system.

Therapeutic Management

Stage-based standard strategies

Management is stratified by stage, and the modalities are three: surgery, radiotherapy, and systemic agents delivered concurrently with radiotherapy. Significantly, the advantageous biology of HPV-positive disease leads to a stage migration within the AJCC 8th edition staging system: tumours that would have been considered advanced under previous criteria are

now categorised as earlier-stage. This shift means that numerous HPV-positive patients now officially fall into “early-stage” categories, despite still having a considerable nodal burden (82, 83).

For early-stage disease (cT1–T2, N0–N1), a single-modality approach is preferred, as adding a second modality increases toxicity without clear benefit. The choice lies between primary radiotherapy and primary transoral surgery, and, critically, there is no high-level evidence that either is superior for oncologic outcome (84, 85). The decision is therefore driven by anticipated functional result, tumour accessibility, and institutional expertise. Definitive radiotherapy to the primary and involved nodes is typically delivered as intensity-modulated radiotherapy (IMRT) to approximately 70 Gy in 35 fractions over seven weeks, a technique that conforms dose to target while sparing critical structures such as the parotid glands, constrictor muscles, and larynx (86, 87).

For locally advanced disease (stage III, or bulky nodal involvement), single-modality treatment is insufficient, and combined-modality therapy becomes standard. The two principal paradigms are definitive concurrent chemoradiotherapy and primary surgery followed by risk-adapted adjuvant therapy (88). The concurrent chemoradiotherapy backbone pairs IMRT with high-dose cisplatin, the cornerstone systemic agent, classically 100 mg/m² intravenously on days 1, 22, and 43 of radiotherapy (89). Where a patient is unfit for high-dose cisplatin, European guidance permits alternatives: carboplatin combined with 5-fluorouracil, cetuximab concurrent with radiotherapy, or altered fractionation radiotherapy (hyper-fractionated or accelerated) without chemotherapy (90). A practical pharmacogenomic caveat applies whenever fluoropyrimidines are used: DPYD genotyping for dihydropyrimidine dehydrogenase deficiency should precede 5-FU administration to avoid catastrophic toxicity in poor metabolizers (91).

Systemic agents by pharmacotherapeutic class

Cisplatin remains the irreplaceable radiosensitizer in this disease. Mechanistically, it forms intra- and interstrand DNA crosslinks, principally at adjacent guanines, that obstruct replication and transcription; in the radiotherapy context, it impairs repair of radiation-induced DNA damage and synchronises cells into radiosensitive phases, producing supra-additive cytotoxicity (92). Its dose-limiting toxicities are equally characteristic: cumulative nephrotoxicity (requiring vigorous hydration), ototoxicity (high-frequency sensorineural hearing loss, frequently permanent), peripheral neuropathy, myelosuppression, and severe emetogenicity (93). Weekly low-dose cisplatin (40 mg/m²) is used in some centres as a less toxic schedule, though the three-weekly high-dose regimen retains the most robust evidence in the definitive setting (94).

Carboplatin is the principal alternative for the substantial minority of patients rendered cisplatin-ineligible by renal impairment, pre-existing sensorineural hearing loss, neuropathy, or advanced age (95, 96). As a second-generation platinum analogue, it shares cisplatin's mechanism, forming platinum-DNA adducts that impede replication and transcription, but its markedly slower aquation kinetics translate into a distinct and generally more favourable toxicity profile: substantially less nephrotoxicity, ototoxicity, neurotoxicity, and emesis, at the cost of dose-limiting myelosuppression, particularly thrombocytopenia (97). Its dosage *via* renal-clearance-based AUC targeting (Calvert formula) as opposed to body-surface area is similarly based on this kinetic difference. Carboplatin is a lesser radiosensitizer than cisplatin, which is an important warning (98). A meta-analysis of moderate-to-advanced head and neck squamous cell carcinoma found cisplatin-based chemoradiotherapy to confer a significant 5-year overall survival advantage over carboplatin-based treatment (HR = 0.67), with the benefit most pronounced in non-nasopharyngeal sites (99). Consequently, carboplatin should be understood not as an equivalent but as a pragmatic compromise, reserved for patients who cannot tolerate cisplatin, in whom a modest efficacy sacrifice is accepted to permit deliverable, tolerable treatment.

Cetuximab is a chimeric monoclonal antibody against the epidermal growth factor receptor (EGFR), which is overexpressed in most head and neck cancers. By binding the receptor's extracellular domain, it blocks ligand-induced dimerisation and downstream RAS-RAF-MAPK and PI3K-AKT signalling, induces receptor internalisation, and can recruit antibody-dependent cellular cytotoxicity (100).

Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, are anti-PD-1 antibodies that release the brake imposed on cytotoxic T cells by the PD-1/PD-L1 axis (101). In the recurrent or metastatic setting, they are firmly established: pembrolizumab (with or without chemotherapy) is a first-line standard, and nivolumab is both EMA- and FDA-approved for platinum-refractory recurrent/metastatic disease, having demonstrated a survival advantage over single-agent chemotherapy (102, 103).

Antimetabolites, such as 5-fluorouracil (5-FU), play a supportive role in this disease rather than acting independently. 5-FU is a fluoropyrimidine that, after undergoing intracellular conversion to its active metabolites, inhibits thymidylate synthase, leading to a depletion of the thymidine pool necessary for DNA synthesis. Additionally, it incorporates nucleotides into RNA and DNA, with these effects being maximised through continuous infusion due to the drug's short plasma half- life (104). It is never used as a single concurrent radiosensitizer in oropharyngeal carcinoma but appears in two combination contexts: with carboplatin as a cisplatin-sparing concurrent regimen, and as a component of taxane-based induction (105). A pertinent observation is that carboplatin/5-

FU combinations, while efficacious, are associated with considerable acute mucosal and haematological toxicity and higher rates of chemotherapy discontinuation, which may itself compromise outcome (105).

Taxanes, docetaxel and paclitaxel, act through a mechanism orthogonal to the platinums and antimetabolites: they bind the β-tubulin subunit of microtubules and stabilise them against depolymerisation, thereby arresting cells at the G2/M transition, the most radiosensitive phase of the cycle (106). Their principal role is within induction chemotherapy, where the triplet of a taxane, cisplatin, and 5-fluorouracil (TPF) is the reference regimen, having demonstrated superiority over cisplatin/5-FU alone in the induction setting (107, 108). However, the addition of TPF induction to concurrent chemoradiotherapy has repeatedly failed to demonstrate a survival benefit over chemo-radiotherapy alone, while adding substantial toxicity, notably grade 3/4 neutropenia and treatment-related deaths (109, 110). Induction, therefore, remains investigational rather than standard. Its most compelling contemporary application is precisely in de-escalation: response to induction is used as a biological triage tool, selecting favourable responders for reduced-dose subsequent therapy, an approach under active study in HPV-positive oropharyngeal cancer, frequently now incorporating well-tolerated carboplatin/paclitaxel doublets (which show comparable activity to TPF with less toxicity) and, increasingly, an anti-PD-1 antibody (111, 112).

Surgical management

The surgical revolution in this disease is transoral robotic surgery (TORS). Historically, accessing the oropharynx required morbid open approaches with mandibulotomy (splitting the jaw) and pharyngotomy, procedures that devastated swallowing and speech. TORS, performed through the open mouth with a robotic platform providing magnified three-dimensional visualisation and wristed instrumentation, allows precise resection of tonsillar and tongue-base tumours without external incisions, preserving function and shortening recovery time (113). It is best suited to favourable-stage primaries with adequate exposure; very large or deeply infiltrative (T4) tumours, or those abutting major vessels, remain poor robotic candidates (114).

Surgery of the primary is almost always accompanied by neck dissection, because HPV-positive OPSCC characteristically presents with early and frequently cystic cervical nodal metastasis. A selective neck dissection typically clears levels II - IV, the echelon nodes draining the oropharynx, both to remove metastatic disease and to provide the pathological nodal staging that guides adjuvant decisions (115, 116). For the minority of cases requiring extensive resection, free-flap reconstruction, most commonly the radial forearm free flap for thin, pliable mucosal defects, or the anterolateral thigh flap for bulkier defects, restores the resected volume using microvascular tissue transfer, reanastomosing the flap's vessels to the neck vasculature (117). In well-selected early-stage HPV-positive disease, however, the trajectory is toward avoiding such extensive reconstruction altogether (118). The decisive surgical insight, embodied in the ECOG-ACRIN Cancer Research Group Trial (E3311), is that TORS is valuable not merely as a resection technique but as a pathological staging tool that can rationally direct and reduce adjuvant therapy (119).

Treatment toxicity, quality of life and the rationale for de-escalation

The entire de-escalation movement is built on a single clinical reality: HPV-positive OPSCC strikes patients who are typically a decade or more younger than HPV-negative patients and who, once cured, may live for many decades bearing the permanent sequelae of intensive treatment (120). Chemoradiotherapy of the oropharynx produces xerostomia (permanent dry mouth from salivary gland injury), dysphagia that, in severe cases, mandates long-term gastrostomy tube dependence, radiation-induced fibrosis of the neck, osteoradionecrosis of the mandible, dysgeusia, hypothyroidism, and, with cisplatin, lifelong hearing loss and neuropathy. When a young patient achieves a cure but cannot swallow normally, the cure is incomplete (87, 121, 122).

The logic of de-escalation is, therefore, to subtract toxicity without subtracting cure. Four strategies have been pursued: substituting cisplatin with a gentler agent, reducing radiotherapy dose or volume, using induction chemotherapy to select responders for lighter treatment, and using minimally invasive surgery to reduce adjuvant intensity (123).

Two landmark randomised trials, RTOG 1016 (North America) and De-ESCALaTE HPV (United Kingdom), tested whether replacing cisplatin with cetuximab, alongside radiotherapy, could preserve survival while reducing toxicity. Both failed, and instructively so. In De-ESCALaTE, overall toxicity was not reduced by cetuximab, whereas cisplatin was clearly superior for survival: 2-year overall survival of roughly 97.5% *versus* approximately 90%, with significantly fewer recurrences favouring cisplatin (124). RTOG 1016, a non-inferiority trial, showed that cetuximab failed to meet non-inferiority criteria, with inferior overall and progression-free survival; the recently matured ten-year follow-up, presented in 2025, confirmed the durable advantage of cisplatin (124). The clear conclusion, reflected in European guidelines and the framework established by the Head and Neck Cancer International Group, is that cetuximab should not be used as a substitute for cisplatin in de-escalation strategies. Furthermore, outcomes in this disease are heavily dependent on appropriate therapy (125, 126).

The second-generation strategies are more promising but remain unproven. The surgical approach exemplified

by ECOG 3311 used TORS plus neck dissection to pathologically stratify intermediate-risk patients, then assigned reduced-dose adjuvant radio-therapy (50 Gy) to those with intermediate-risk pathology, achieving excellent disease control with reduced morbidity, and establishing proof of principle that pathology-guided dose reduction is feasible (119). The radiotherapy-focused approach pioneered by Chera and colleagues tested markedly reduced-dose chemo-radiotherapy (60 Gy with concurrent low-dose cisplatin) in carefully selected low-risk patients (limited smoking history, favourable stage), again reporting high control rates (127). These approaches maintain an important discipline that is lacking in the cetuximab experiments: they focus on reducing the dose instead of substituting the effective drug, and they limit de-escalation to precisely defined low-risk sub-groups.

Consequently, de-escalation is biologically logical and continues to be the most dynamic area of investigation in the field. Nonetheless, the unsuccessful outcomes of the substitution trials illustrated that milder does not equate to less effective, and, according to current European guidelines, de-escalated regimens should be confined to clinical trials rather than implemented in routine practice.

Emerging Directions

For an extended period, the application of immunotherapy in head and neck cancer was limited to cases of incurable recurrent or metastatic disease. That boundary has now been transcended. The phase III KEYNOTE-689 trial, reported in 2025, integrated the anti-PD-1 antibody pembrolizumab into curative-intent treatment of resectable locally advanced HNSCC, administered as neoadjuvant therapy before surgery and continued as adjuvant therapy alongside radiotherapy with or without cisplatin (128). The trial met its primary endpoint, significantly improving event-free survival (median EFS approximately 51.8 *versus* 30.4 months), with benefit observed across PD-L1 subgroups and accompanied by meaningful major pathological responses to neoadjuvant priming. On the strength of these data, pembrolizumab gained regulatory approval (initially from the FDA, June 2025) for resectable locally advanced HNSCC expressing PD-L1 with a combined positive score ≥ 1, marking the first practice-changing addition to curative therapy for this disease in two decades.

However, there are two limitations, both pertinent to the HPV-positive population in particular. First, KEYNOTE-689 enrolled HNSCC broadly (oral cavity, larynx, hypopharynx, and oropharynx), and the benefit was less pronounced in the PD-L1 CPS < 10 subgroup, so the magnitude of advantage for any individual HPV-positive oropharyngeal patient remains unresolved. Second, and conceptually important, immunotherapy in HPV-positive disease points in two opposite strategic directions simultaneously: It has the potential to enhance treatment for the challenging subset of patients who experience recurrence. Additionally, due to its relatively favourable tolerance and the presence of tumour-specific antigens from HPV oncoproteins (specifically the continuously expressed E6 and E7), it may ultimately pave the way for a novel approach to de-escalation, facilitating a reduction in the use of cytotoxic chemoradiotherapy (129). Therapeutic HPV E6/E7 vaccines and adoptive T-cell approaches directed at these viral antigens extend this logic further and are under active investigation (130).

Prognosis

The primary prognostic factor in oropharyngeal cancer is HPV status, and the extent of its impact is extremely significant. In the landmark RTOG 0129 analysis that first quantified the divide, patients with HPV-positive disease had a 58% reduction in the risk of death at three years compared with HPV-negative patients, with three-year overall survival of roughly 82% *versus* 57% (131). This benefit also applies to recurrence: HPV-driven tumours tend to recur less often and, when they do, they occur at a later stage. The benefit is substantial enough that it endures across various treatment approaches and supports the positive results observed even in the de-escalation and substitution trials mentioned earlier, where the cisplatin arms of RTOG 1016 and De-ESCALaTE reached two-year survival rates nearing or surpassing 90% (132).

This favourable behaviour is the result of numerous biological mechanisms that are converging. First, and most importantly, HPV-positive tumours retain wild-type p53, functionally suppressed by E6 but not mutated, so that when E6 expression is reduced, or the cell is stressed by therapy, the intact apoptotic machinery can be reactivated, rendering these cells intrinsically more sensitive to the DNA damage inflicted by radiotherapy and cisplatin (133). Second, these tumours carry a comparatively low burden of somatic mutations and lack the widespread field cancerization that plagues tobacco-driven disease, reducing the reservoir of second primaries and treatment-resistant clones (134). Third, the constitutively expressed viral oncoproteins E6 and E7 furnish tumour-specific antigens that provoke a more active antitumor immune response, often reflected in dense tumour-infiltrating lymphocytes that correlate with better outcomes (135).

Still, two limitations exist: heavy tobacco exposure measurably erodes the HPV survival advantage, and the favourable biology does not extend to the p16-positive/HPV-negative discordant subgroup (136).

Conclusions

HPV-positive oropharyngeal carcinoma has emerged as a distinct disease entity, defined molecularly by

E6- and E7-driven inactivation of p53 and Rb, and clinically by a younger patient population and a markedly favourable prognosis. Yet this favourable biology has not yet translated into a separate treatment standard. The central therapeutic lesson of the past decade is cautionary: the failure of the cetuximab-substitution trials demonstrated that milder must never mean less effective, and European guidelines accordingly maintain cisplatin-based chemoradiotherapy as standard, reserving de-escalation for clinical trials. The most pressing therapeutic priorities are, therefore, to validate pathology- and dose-guided de-escalation in rigorously selected low-risk patients, and to define the role of immunotherapy, now established in the curative setting by KEYNOTE-689, as either an intensification or a de-escalation tool. Alongside these, the absence of a validated screening method and incomplete vaccine uptake, particularly in men, remain the defining unmet needs.

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