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# Advancing Precision Oncology in the USA: A Literature Review of EGFR, MYC, and RAS Alterations in Head and Neck Cancers

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## *Abstract*

*Head and neck cancers (HNCs) constitute a diverse group of malignancies characterized by complex molecular alterations that contribute to tumor initiation, progression, therapeutic resistance, and clinical heterogeneity. In the era of precision oncology in the United States, a comprehensive understanding of key oncogenic drivers, particularly EGFR, MYC, and RAS, has become increasingly important for*

*improving risk stratification, early diagnosis, prognostic assessment, and the development of personalized therapeutic strategies. These genes regulate critical cellular processes, including proliferation, apoptosis, angiogenesis, and signal transduction, and their dysregulation is closely associated with aggressive tumor behaviour and variable treatment responses. This literature review synthesizes current evidence on the molecular alterations, biological significance, and clinical implications of EGFR, MYC, and RAS in head and neck cancers, with an emphasis on their role as diagnostic, prognostic, and predictive biomarkers. Furthermore, it highlights recent advances in targeted therapies and precision medicine approaches aimed at improving patient outcomes. By consolidating contemporary molecular insights, this review underscores the growing need to integrate genomic profiling into routine clinical practice to facilitate individualized treatment planning and advance precision oncology for patients with head and neck cancers in the United States.*

**Keywords:** Head and neck cancer, Precision Oncology, oncogenes, Targeted Therapy, United States.

## Introduction

Head and neck cancer (HNC) represents one of the top common types with incidence of greater than half a million cases diagnosed annually. Oral, pharyngeal, and laryngeal squamous cell carcinoma (SCC) represent almost 90% of the cases. Surgical resection, radiotherapy or both have been used over the past few decades [1,2]. Head and neck cancer (HNC) is a diverse disease that impacts different areas of the upper aerodigestive tract, including various histological types and anatomical locations [3]. The realization that the epidermal growth factor receptor (EGFR) is overexpressed and structurally altered in HNSCC and plays a role in its pathogenesis and clinical course has provided the rationale for the development and implementation of EGFR- targeted therapies [4]. The epidermal growth factor receptor (EGFR) is a transmembrane receptor belonging to the group of receptor tyrosine kinases that forward extracellular signals via phosphorylation cascades, which finally arouse cellular responses [5]. The cytoplasmic pathway is mediated by the phosphorylation of four key modules: RAS (a small GTPase family first identified in this context), PI3K (phosphoinositide 3-kinase), PLC-γ (phospholipase C gamma), and STAT3 (signal transducer and activator of transcription 3) [6]. In parallel, the MYC oncogene functions as a pivotal transcriptional regulator that governs cell proliferation, metabolism, and apoptosis, thereby contributing significantly to tumorigenesis in head and neck cancers. Aberrant MYC activation—through gene amplification or dysregulated signalling—facilitates uncontrolled cellular growth and enhances malignant progression. Furthermore, its interaction with downstream pathways of EGFR and RAS underscores its role in promoting tumor aggressiveness and therapeutic resistance. The RAS family of proto-oncogenes, comprising **HRAS, KRAS, and NRAS**, represents another critical molecular component involved in the pathogenesis of head and neck cancers [7]. These genes encode small guanosine triphosphate (GTP)-binding proteins that function as molecular switches regulating intracellular signalling pathways responsible for cell proliferation, differentiation, survival, and migration. Activating mutations, particularly in **HRAS**, have been identified in a subset of head and neck squamous cell carcinomas (HNSCC), resulting in persistent activation of downstream signalling cascades such

as the RAF/MEK/ERK and PI3K/AKT/mTOR pathways. Such molecular alterations contribute to uncontrolled cellular proliferation, enhanced metastatic potential, resistance to apoptosis, and diminished responsiveness to conventional therapeutic modalities.

Recent advances in molecular biology and next-generation sequencing technologies have substantially improved the understanding of the genomic landscape of HNSCC. Comprehensive molecular profiling has revealed that genetic alterations involving **EGFR, MYC and RAS** are frequently accompanied by dysregulation of multiple signalling networks, collectively driving tumour initiation, progression, invasion, and treatment resistance [8]. These discoveries have shifted the paradigm of cancer management from conventional histopathology-based approaches toward precision oncology, wherein therapeutic decisions are guided by the unique molecular characteristics of an individual's tumour. Such an approach facilitates the identification of predictive biomarkers, enables patient stratification, and supports the development of targeted therapies with improved efficacy and reduced treatment-related toxicity.

In the United States, precision oncology has rapidly evolved through the integration of genomic sequencing, molecular diagnostics, artificial intelligence-assisted genomic interpretation, and biomarker-driven clinical trials. Despite significant progress, considerable challenges remain, including tumour heterogeneity, acquired therapeutic resistance, limited efficacy of targeted agents in selected patient populations, and disparities in access to precision medicine. Therefore, a comprehensive understanding of the molecular alterations involving EGFR, MYC, and RAS is essential for identifying novel therapeutic targets and optimizing personalized treatment strategies [9].

This literature review aims to comprehensively summarize the current evidence regarding the molecular biology, genetic alterations, and clinical significance of EGFR, MYC, and RAS in head and neck cancers. Furthermore, it highlights recent advances in targeted therapeutics, discusses ongoing challenges in precision oncology, and explores future directions for translating molecular discoveries into individualized clinical care, thereby contributing to improved patient outcomes and advancing precision oncology in the United States.

## Epidemiology and Molecular Heterogeneity of Head and Neck Cancer

Head and neck squamous cell carcinoma (HNSCC) remains a significant public health challenge in the United States, accounting for thousands of newly diagnosed cases and cancer-related deaths each year. The disease encompasses a biologically diverse group of malignancies arising from the oral cavity, oropharynx, hypopharynx, and larynx, with distinct etiological and molecular characteristics [10]. While tobacco and alcohol consumption have historically been the principal risk factors, the incidence of human papillomavirus (HPV)-associated oropharyngeal cancers has risen substantially, giving rise to a clinically and molecularly distinct subtype with improved prognosis and enhanced responsiveness to therapy. In contrast, HPV-negative tumors are frequently characterized by extensive genomic instability, aggressive clinical behaviour, and poorer treatment outcomes. Molecular heterogeneity in HNSCC is further driven by alterations in oncogenes such as EGFR, MYC, and RAS, along with numerous co-occurring genetic and epigenetic abnormalities. Moreover, considerable in-

terpatient and intratumoral heterogeneity contributes to variable therapeutic responses and the emergence of treatment resistance [11]. Understanding these epidemiological trends and molecular complexities is fundamental to advancing precision oncology, enabling biomarker-driven patient stratification, personalized therapeutic interventions, and improved clinical outcomes for patients with head and neck cancers in the United States.

## Understanding Molecular Landscape of Head and Neck Cancers

EGFR is a transmembrane protein comprised of an extracellular ligand-binding domain (ECD), a transmembrane domain (TD), a juxta membrane (JM) segment, a tyrosine kinase domain (TKD), and a C-terminal regulatory tail [7,8]. Since EGFR plays a critical role in regulating various cellular processes, oncogenic mutations in any of these domains result in aberrant expression and/or dysregulated signalling while also altering responses to EGFR targeting agents [9].

The RAS gene superfamily comprises over 170 RAS related proteins [10]. RAS proteins are small GTP-binding proteins that play essential roles in cell signalling and communication [11]. While RAS proteins share similar functions, their specific roles can vary within cells. They activate adenylate cyclase, leading to cAMP production and initiating various downstream processes [6]. These genes are crucial for key cellular signalling pathways that regulate the cell cycle, cytoskeletal dynamics, differentiation, proliferation, survival, molecular and vesicular transport, and cell growth [12].

The avian myelocytomatosis viral oncogene homolog (MYC) is one of the most frequently mutated oncogenes, and its overexpression is strongly associated with cancer, making it a major focus of research [13]. This critical gene is located on chromosome 8 and regulates up to 15% of all genes [14]. MYC has paralogues, such as L-MYC and N-MYC, located on chromosomes 1 and 2, respectively [15,16]. These proteins share several highly conserved, functionally important regions, which are similarly organized [6]. L-MYC is expressed and active in dendritic cells, gastrointestinal cells, and lung cells. N-MYC, on the other hand, is expressed in neural stem cells, where it promotes rapid cell proliferation in stem cells and neuroendocrine tissues in the developing brain [17,18]. As a transcription factor, the MYC protein is involved in the regulation of cell proliferation and apoptosis [6]. The ability of MYC to regulate apoptotic cell death results from the coordinated activation of MYC and several protein partners, such as myc-associated factor X (MAX), which facilitates DNA binding and activates transcription or binding of Max dimerization protein/Max interfactor/Max binding protein antagonists [19].

EGFR, MYC, and RAS (Figure 1) are key oncogenes implicated in head and neck carcinogenesis through dysregulation of cell growth and survival pathways. **EGFR** (epidermal growth factor receptor) is a transmembrane tyrosine kinase that promotes proliferation, angiogenesis, and resistance to apoptosis when overexpressed. **MYC** is a nuclear transcription factor that drives uncontrolled cell cycle progression, metabolic reprogramming, and genomic instability. **RAS** genes encode small GTP-binding proteins that regulate signalling cascades such as MAPK and PI3K; activating mutations result in persistent proliferative signalling. Together, these genes interact within complex networks, enhancing tumor initiation, progression, and therapeutic resistance in head and neck cancers [18].

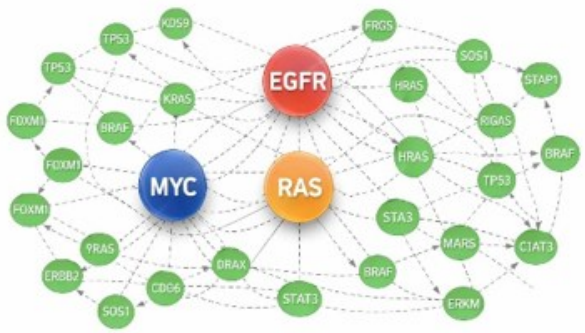


Figure 1: Networking of Onco genes

Beyond their individual oncogenic functions, EGFR, MYC, and RAS participate in an intricate and interconnected signalling network that orchestrates multiple hallmarks of cancer. Aberrant activation of EGFR frequently initiates downstream signalling through the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways, ultimately influencing MYC transcriptional activity and promoting uncontrolled cellular proliferation, survival, angiogenesis, epithelial-mesenchymal transition, and metastatic dissemination. This molecular crosstalk not only accelerates tumour progression but also contributes to intratumoral heterogeneity and the emergence of therapeutic resistance, which remain significant barriers to successful clinical management of head and neck cancers [16].

Advances in high-throughput genomic technologies, including next-generation sequencing (NGS), whole-exome sequencing, transcriptomic profiling, and comprehensive molecular biomarker analyses, have transformed the understanding of the molecular landscape of head and neck squamous cell carcinoma [17]. These technologies have enabled the identification of recurrent genomic alterations, co-occurring mutations, copy number variations, and aberrant signalling pathways associated with EGFR, MYC, and RAS. Consequently, molecular profiling has become an indispensable component of precision oncology by facilitating patient stratification, prognostic risk assessment, prediction of therapeutic response, and selection of individualized treatment strategies.

In the United States, the incorporation of molecular diagnostics into routine oncologic practice has accelerated the transition toward biomarker-driven precision medicine. Comprehensive genomic testing increasingly guides therapeutic decision-making by identifying patients who are most likely to benefit from targeted therapies, combination treatment regimens, and enrolment in precision oncology clinical trials. Simultaneously, ongoing translational research is exploring innovative therapeutic approaches, including selective kinase inhibitors, monoclonal antibodies, synthetic lethality strategies, epigenetic modulators, immunotherapy combinations, and gene-editing technologies directed against dysregulated EGFR, MYC, and RAS signalling pathways [19].

Despite these remarkable advances, several challenges continue to limit the full clinical implementation of precision oncology. Tumour heterogeneity, dynamic genomic evolution, compensatory signalling mechanisms, acquired drug resistance, and limited actionable mutations in certain patient populations necessitate continuous research into novel biomarkers and therapeutic targets [19]. A comprehensive understanding of the molecular interactions among EGFR, MYC, and RAS is therefore essential for developing more effective precision-based therapeutic strategies, improving patient selection, overcoming treatment resistance, and ultimately enhancing survival outcomes for patients with head and neck cancers in the United States.

## Molecular Biomarkers In Precision Oncology

Molecular biomarkers have become indispensable in precision oncology by enabling early diagnosis, prognostic assessment, prediction of therapeutic response, and individualized treatment planning for patients with head and neck cancers. **Diagnostic biomarkers** facilitate the early detection and molecular classification of tumors by identifying genetic and protein alterations, including **EGFR, MYC, and RAS**, thereby improving diagnostic accuracy. **Prognostic biomarkers** provide information regarding disease progression, recurrence risk, and overall survival independent of treatment, assisting clinicians in stratifying patients according to clinical outcomes [36]. In contrast, **predictive biomarkers** identify patients who are most likely to respond to specific targeted therapies or immunotherapeutic agents, thereby optimizing treatment selection and minimizing unnecessary toxicity.

**Companion diagnostics** are validated molecular assays that detect actionable genetic alterations and guide the use of targeted therapies, ensuring that patients receive the most appropriate personalized treatment. In recent years, **liquid biopsy** has emerged as a minimally invasive alternative to tissue biopsy, enabling real-time monitoring of tumour evolution and therapeutic response through analysis of blood-based biomarkers. **Circulating tumor DNA (ctDNA)**, released by apoptotic or necrotic tumour cells, provides valuable information regarding tumour burden, minimal residual disease, and emerging resistance mutations [38]. **Exosomes**, small extracellular vesicles secreted by tumour cells, carry DNA, RNA, proteins, and microRNAs that reflect the molecular characteristics of the primary tumour and serve as promising biomarkers for diagnosis and disease monitoring. Additionally, **circulating tumour cells (CTCs)**, which detach from primary or metastatic lesions and enter the bloodstream, provide insights into metastatic potential, tumour heterogeneity, and treatment response [37]. Collectively, these molecular biomarkers have transformed precision oncology in the United States by facilitating biomarker-guided therapeutic decision-making, real-time disease surveillance, and the development of personalized treatment strategies for patients with head and neck cancers.

## Therapeutic Implications And Targeted Strategies

The concerted efforts of clinical trial correlative studies to collect and molecularly analyze tumor specimens and assess correlations with clinical response to targeted therapeutics are ongoing [19]. The growing understanding of the molecular alterations involving **EGFR, MYC, and RAS** has significantly transformed the therapeutic landscape of head and neck cancers, shifting treatment paradigms from conventional approaches toward biomarker-driven precision oncology. Among these oncogenes, **EGFR** remains the most extensively investigated therapeutic target, with monoclonal antibodies and tyrosine kinase inhibitors demonstrating clinical benefit in selected patients [20]. However, variability in treatment response, intrinsic resistance, and the development of acquired resistance highlight the need for molecular profiling to identify patients most likely to benefit from EGFR-targeted therapies. Consequently, genomic characterization has become increasingly important for optimizing treatment selection and improving therapeutic outcomes.

Although direct targeting of **MYC** has historically been challenging due to its structural and functional characteristics, recent advances have led to the

development of indirect therapeutic strategies aimed at inhibiting MYC transcription, disrupting MYC-MAX dimerization, modulating epigenetic regulators, and exploiting synthetic lethality. Similarly, therapeutic approaches targeting aberrant **RAS** signalling have evolved considerably with the emergence of selective inhibitors and downstream pathway blockade, particularly targeting the RAF/MEK/ERK and PI3K/AKT/mTOR signalling cascades [21]. Combination treatment strategies integrating targeted agents with immunotherapy, chemotherapy, and radiotherapy are also being actively investigated to overcome tumour heterogeneity and therapeutic resistance.

In the United States, Continued investigation of EGFR, MYC, and RAS alterations, together with the identification of novel predictive biomarkers and resistance mechanisms, is expected to further refine targeted treatment strategies, improve clinical response, reduce treatment-related toxicity, and ultimately enhance survival and quality of life for patients with head and neck cancers.

**Indirect targeting of EGFR, MYC and RAS** is achieved mainly through inhibition of upstream activators, inhibition of EGFR, MYC and RAS association with the plasma membrane, and inhibition of effector signalling pathways [20]. The growing understanding of the molecular alterations involving **EGFR, MYC, and RAS** has significantly transformed the therapeutic landscape of head and neck cancers, shifting treatment paradigms from conventional approaches toward biomarker-driven precision oncology. Among these oncogenes, **EGFR** remains the most extensively investigated therapeutic target, with monoclonal antibodies and tyrosine kinase inhibitors demonstrating clinical benefit in selected patients [22]. However, variability in treatment response, intrinsic resistance, and the development of acquired resistance highlight the need for molecular profiling to identify patients most likely to benefit from EGFR-targeted therapies. Consequently, genomic characterization has become increasingly important for optimizing treatment selection and improving therapeutic outcomes.

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In the United States, precision oncology initiatives have accelerated the incorporation of comprehensive genomic profiling, biomarker-guided clinical trials, and multidisciplinary treatment planning into routine oncologic practice. These advances have enabled a more individualized therapeutic approach based on the molecular characteristics of each patient's tumour.

**Proton radiotherapy:** Proton beam therapy was introduced in radiotherapy to be used when the cancer is close to critical anatomical structures be-

cause the beam energy can be aimed at an exact depth, with consequent dose decrease. Therefore, it is different than external photon (x-ray) radiotherapy in which it can keep the same radiation dose for the normal adjacent tissues when the radiation dose is escalating to the tumor area [21]. Recent technological advancements have positioned proton radiotherapy as an important component of precision oncology for the management of head and neck cancers. The unique physical property of proton beams, known as the **Bragg peak**, enables the majority of the radiation dose to be deposited directly within the tumour while minimizing the exit dose to surrounding normal tissues [23]. This Dosimetric advantage is particularly valuable in head and neck malignancies, where tumors are frequently located adjacent to radiosensitive structures such as the salivary glands, spinal cord, optic apparatus, brainstem, cochlea, mandible, and oral cavity. By reducing unnecessary radiation exposure to these critical organs, proton therapy has the potential to preserve normal tissue function and improve patients' quality of life.

Clinical studies have demonstrated that proton therapy is associated with lower rates of treatment-related toxicities, including xerostomia, dysphagia, mucositis, osteoradionecrosis, hearing impairment, and long-term swallowing dysfunction, while maintaining tumour control rates comparable to advanced photon-based techniques such as intensity-modulated radiotherapy (IMRT) [24]. Consequently, patients may experience fewer treatment interruptions, improved nutritional status, and better functional recovery following therapy.

In the United States, proton radiotherapy has become increasingly integrated into comprehensive cancer centres and multidisciplinary precision oncology programs. The combination of advanced imaging, treatment planning software, and molecular characterization of tumours allows clinicians to deliver highly individualized radiation treatment tailored to each patient's anatomical and biological profile [23]. Ongoing clinical trials continue to evaluate the optimal integration of proton therapy with targeted therapies, immunotherapy, and biomarker-guided treatment strategies, with the goal of maximizing therapeutic efficacy while minimizing long-term morbidity in patients with head and neck cancers.

**Cellular and cancer response to radiation:** When high-voltage x-ray penetrates the tissues, it ionizes the oxygen and produces free oxygen radicals and cancer death [22]. Therefore, this high-voltage x-ray can damage the genetic material of the cells (DNA), which blocks division and proliferation of oncogenes [21]. The biological response of cancer cells to radiation is determined by the extent of DNA damage and the cellular capacity to repair these lesions. Ionizing radiation primarily induces single-strand and double-strand DNA breaks, with double-strand breaks representing the most lethal form of genetic damage. In addition to direct DNA injury, radiation generates reactive oxygen species (ROS), which further amplify oxidative stress, damage cellular membranes and proteins, and enhance tumour cell death. Activation of DNA damage response pathways involving proteins such as **ATM, ATR, p53, and DNA-dependent protein kinase (DNA-PK)** leads to cell cycle arrest, apoptosis, senescence, mitotic catastrophe, or permanent loss of reproductive capacity.

In head and neck cancers, the molecular status of oncogenes such as **EGFR, MYC, and RAS** significantly influences radiosensitivity. Overexpression

of EGFR enhances DNA repair mechanisms and promotes tumour cell survival, thereby contributing to radioresistance [26]. Likewise, aberrant activation of MYC and RAS signalling supports rapid cellular proliferation, metabolic adaptation, and resistance to apoptosis following radiation exposure. These molecular mechanisms have prompted the development of combined treatment strategies integrating radiotherapy with targeted molecular inhibitors to enhance radiosensitivity, overcome therapeutic resistance, and improve local tumour control while minimizing damage to surrounding normal tissues.

**CTLA-4 antibodies:** Ipilimumab and tremelimumab are mono-antibodies, which block CTLA-4 and are currently being tested for efficacy in HNSCC, despite promising results in other tumors [23]. Wang et al. found that blocking the CTLA-4 receptor can activate CD8+ T cells, increase production of IFN-$\gamma$ and TNF-$\alpha$, activate the STAT1/IRF1 axis and trigger tumor cell heat death in HNSCC [24,25]. The therapeutic rationale for CTLA-4 inhibition in head and neck cancers is based on its ability to enhance T-cell priming and restore effective antitumour immune responses. By preventing the interaction between CTLA-4 and its ligands (CD80/CD86), CTLA-4 antibodies promote sustained activation and proliferation of cytotoxic T lymphocytes, thereby improving immune-mediated tumour eradication. Recent clinical investigations have explored the combination of CTLA-4 inhibitors with programmed cell death protein-1 (PD-1) inhibitors, radiotherapy, chemotherapy, and EGFR-targeted agents to achieve synergistic antitumour effects [29]. Although response rates have been variable, ongoing biomarker-driven clinical trials in the United States aim to identify patients who are most likely to benefit from CTLA-4 blockade, supporting the broader integration of immune checkpoint inhibition into precision oncology strategies for head and neck cancers.

**Targeted therapy:** Traditional treatments for HNC primarily include surgery, RT, and CT. Currently, surgery remains the cornerstone of HNC treatment except for nasopharynx cancer. Traditional treatments for HNC primarily include surgery, RT, and CT. Currently, surgery remains the cornerstone of HNC treatment except for nasopharynx cancer [25]. However, as our understanding of the molecular characteristics and pathogenesis of HNC has deepened over the past decade, treatment strategies have evolved significantly. This evolution has introduced targeted therapy, immunotherapy and gene therapy, either alone or in combination with traditional methods like surgery, RT, or CT [26-33]. Targeted therapy aims to selectively inhibit molecular pathways that are essential for tumour growth, proliferation, angiogenesis, invasion, and metastatic progression while minimizing damage to normal tissues. In head and neck cancers, **EGFR** remains the most extensively validated therapeutic target because of its frequent overexpression and its central role in activating downstream signalling pathways, including **RAS/RAF/MEK/ERK**, **PI3K/AKT/mTOR**, and **JAK/STAT** [27,28]. Monoclonal antibodies such as cetuximab and tyrosine kinase inhibitors have demonstrated clinical benefit in selected patients, particularly when combined with radiotherapy or chemotherapy, although therapeutic resistance continues to limit long-term efficacy.

Advances in molecular oncology have also expanded therapeutic opportunities beyond EGFR. Aberrant activation of **RAS** signalling has prompted the investigation of MEK, ERK, and PI3K inhibitors,

while novel strategies targeting **MYC** focus on disrupting transcriptional activity, inhibiting MYC-MAX interactions, modulating epigenetic regulators, and exploiting synthetic lethality [31]. Although direct MYC inhibition remains challenging, these emerging approaches have shown encouraging preclinical and early clinical results.

In the era of precision oncology, comprehensive genomic profiling and biomarker-driven treatment selection have become integral components of personalized cancer care in the United States. Identification of actionable molecular alterations enables clinicians to tailor therapy according to the genetic profile of individual tumours, thereby improving treatment efficacy and reducing unnecessary toxicity [36]. Furthermore, combination strategies integrating targeted therapy with immunotherapy, radiotherapy, and conventional chemotherapy are being actively evaluated to overcome tumour heterogeneity, prevent acquired resistance, and achieve more durable clinical responses. Continued translational research and biomarker-guided clinical trials are expected to further refine targeted therapeutic approaches and improve survival outcomes for patients with head and neck cancers.

**Molecular targeted therapy:** Compared with the toxicity and drug resistance caused by traditional treatment methods, molecular targeted therapy offers higher selectivity and fewer adverse reactions [34]. By targeting cell surface receptors such as EGFR, VEGFR, HER2, and MET, and their downstream signalling pathways, it is possible to inhibit HNSCC cell proliferation, invasion, and migration [25]. Additionally, targeting epigenetic modification sites like histone acetylation/deacetylation or DNA methylation can inhibit HNSCC migration and proliferation [35]. Recent advances in molecular oncology have expanded the scope of molecular targeted therapy by enabling treatment strategies based on the unique genomic and proteomic profiles of individual tumours. Comprehensive molecular profiling using next-generation sequencing has facilitated the identification of actionable alterations involving **EGFR, MYC, RAS**, PI3K/AKT/mTOR, and other oncogenic pathways, thereby supporting personalized therapeutic decision-making. In addition, combination approaches integrating molecular targeted agents with immunotherapy, radiotherapy, or chemotherapy have demonstrated the potential to enhance treatment efficacy, overcome resistance mechanisms, and improve disease control [29]. As precision oncology continues to evolve in the United States, biomarker-guided molecular targeted therapy is expected to play an increasingly important role in optimizing clinical outcomes and minimizing treatment-related toxicity in patients with head and neck cancers.

**Targeting cell surface receptors:** Cell surface receptors like EGFR, VEGFR, HER2, and MET are overexpressed in HNC, driving tumor growth, cell migration, and metastasis [25]. Inhibiting these surface receptors with targeted agents can interrupt the downstream signalling cascades responsible for oncogene activation, including pathways involving RAS and MYC. This disruption limits abnormal cellular signalling and reduces uncontrolled tumor growth. As a result, such targeted therapies represent an effective approach to restrain the development and progression of head and neck cancer. Among these receptors, **EGFR** remains the most extensively studied and clinically validated therapeutic target in head and neck squamous cell carcinoma because of its frequent overexpression and its pivotal role in regulating cellular proliferation, angiogenesis, invasion, and resistance to apoptosis

[30]. Activation of EGFR stimulates multiple downstream signalling pathways, including **RAS/RAF/MEK/ERK**, **PI3K/AKT/mTOR**, and **JAK/STAT**, all of which contribute to tumour progression and therapeutic resistance [27]. Consequently, inhibition of EGFR using monoclonal antibodies or tyrosine kinase inhibitors has demonstrated significant clinical benefit, particularly when combined with radiotherapy or platinum-based chemotherapy.

Similarly, inhibition of **VEGFR** suppresses tumour angiogenesis by reducing the formation of new blood vessels required for tumour growth and metastatic spread, while targeting **HER2** interferes with receptor-mediated proliferative signalling in selected molecular subtypes of head and neck cancers. Therapeutic inhibition of **MET**, a receptor activated by hepatocyte growth factor, limits tumour cell migration, epithelial-mesenchymal transition, invasion, and distant metastasis [29]. Increasing evidence also suggests that simultaneous inhibition of multiple cell surface receptors may overcome compensatory signalling mechanisms that frequently contribute to treatment resistance. In the era of precision oncology, comprehensive molecular profiling enables identification of patients with receptor-specific alterations, allowing biomarker-guided selection of targeted therapies and facilitating a personalized treatment approach that improves therapeutic efficacy while minimizing unnecessary toxicity.

**Immunotherapy:** Head and neck cancers are characterized by a highly inflammatory tumor microenvironment compared to many other solid malignancies, which enhances their responsiveness to immunotherapeutic approaches. This unique immune landscape provides opportunities for targeted immune-based interventions [32]. Current treatment modalities focus on immune checkpoint inhibitors, adoptive cell transfer, oncolytic virus therapies, cancer vaccines, and various immunomodulatory agents aimed at strengthening anti-tumor immunity. Among the various immunotherapeutic strategies, immune checkpoint inhibitors targeting the programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) pathways have demonstrated the most promising clinical outcomes in recurrent and metastatic head and neck squamous cell carcinoma [35]. By blocking these inhibitory immune checkpoints, these agents restore cytotoxic T-cell activity, enhance tumour antigen recognition, and promote sustained anti-tumour immune responses. In addition, adoptive cell therapies, including tumour-infiltrating lymphocyte (TIL) therapy and chimeric antigen receptor (CAR)-T cell therapy, are being actively investigated to improve immune-mediated tumour eradication [36].

Oncolytic viruses selectively infect and destroy malignant cells while simultaneously stimulating systemic antitumour immunity through the release of tumour-associated antigens. Similarly, therapeutic cancer vaccines are designed to induce durable, antigen-specific immune responses against tumour-associated or viral antigens, particularly in human papillomavirus (HPV)-associated head and neck cancers [31]. Recent advances in precision oncology have further emphasized biomarker-guided immunotherapy, where molecular profiling, tumour mutational burden, PD-L1 expression, and genomic alterations such as EGFR, MYC, and RAS may influence treatment selection and clinical response [38]. Ongoing clinical trials are evaluating combination strategies integrating immunotherapy with

targeted therapy, radiotherapy, and chemotherapy to overcome immune evasion, reduce therapeutic resistance, and improve long-term survival outcomes for patients with head and neck cancers.

**Gene therapy:** Gene therapy has been widely utilized for cancer treatment, significantly enhancing antitumor efficacy. Various gene therapy agents employing the rAd-p53 vector have been used in cancer treatment, with clinical gene therapy [25]. Gene therapy aims to modify the genetic and molecular abnormalities that drive tumor initiation, progression, and therapeutic resistance by restoring normal gene function, silencing oncogenes, or enhancing antitumor immune responses. In head and neck cancers, several gene delivery strategies have been investigated, including viral vectors such as adenoviruses, adeno-associated viruses, lentiviruses, and herpes simplex viruses, as well as non-viral delivery systems utilizing nanoparticles, liposomes, and polymer-based carriers. These approaches enable the targeted delivery of therapeutic genes while minimizing systemic toxicity and improving treatment specificity [39].

Beyond p53 replacement therapy, considerable attention has been directed toward suppressing oncogenic signalling mediated by **EGFR, MYC, and RAS**, which are central molecular drivers of head and neck squamous cell carcinoma. Gene-silencing technologies, including small interfering RNA (siRNA), short hairpin RNA (shRNA), antisense oligonucleotides, and microRNA-based therapeutics, have demonstrated the potential to inhibit the expression of these oncogenes and reduce tumour proliferation, invasion, angiogenesis, and metastatic potential. Furthermore, advances in genome-editing technologies, particularly the **CRISPR-Cas9** system, have created new opportunities for precise correction or disruption of cancer-associated genetic alterations, offering the possibility of highly personalized therapeutic interventions [40].

Recent developments in precision oncology have also promoted the integration of gene therapy with conventional treatment modalities, including surgery, radiotherapy, chemotherapy, immunotherapy, and molecular targeted therapy. Such multimodal approaches aim to enhance tumour sensitivity to treatment, overcome drug resistance, and improve long-term disease control. In the United States, ongoing translational research and biomarker-driven clinical trials are evaluating the safety, efficacy, and clinical applicability of next-generation gene therapies for head and neck cancers. As genomic technologies continue to advance, individualized gene therapy guided by comprehensive molecular profiling is expected to become an increasingly important component of precision oncology, enabling personalized treatment strategies that improve survival while reducing treatment-related toxicity and disease recurrence.

**Epigenetic modification therapy:** Epigenetic alterations are key contributors to the initiation and progression of head and neck cancer. These changes influence gene expression without altering the underlying DNA sequence, thereby promoting tumor development. Therapeutic approaches aimed at reversing such modifications have gained significant attention in recent years [44]. Agents targeting epigenetic mechanisms, particularly DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors, have demonstrated promising outcomes. Both classes of drugs have been widely explored in laboratory as well as clinical settings for HNC management [41]. Among them,

DNMT inhibitors such as azacytidine and decitabine are currently being evaluated in clinical trials. These therapies offer a potential strategy to restore normal gene function and limit cancer progression. Recent advances in cancer epigenetics have demonstrated that aberrant DNA methylation, histone modifications, chromatin remodeling, and dysregulated non-coding RNAs collectively contribute to the silencing of tumour suppressor genes and activation of oncogenic pathways, including **EGFR, MYC, and RAS** signalling [39]. Unlike permanent genetic mutations, epigenetic alterations are potentially reversible, making them attractive therapeutic targets in precision oncology. Restoration of normal epigenetic regulation has been shown to inhibit tumour cell proliferation, induce apoptosis, reduce metastatic potential, and enhance tumour sensitivity to conventional therapies.

In addition to DNMT and HDAC inhibitors, emerging therapeutic strategies targeting bromodomain and extraterminal (BET) proteins, histone methyltransferases, histone demethylases, and enhancer-associated transcriptional regulators are under active investigation [45]. BET inhibitors, in particular, have demonstrated the ability to suppress **MYC** transcription, thereby reducing tumour growth and improving treatment response in preclinical models of head and neck cancer [36]. Furthermore, epigenetic therapies have shown considerable promise when combined with immunotherapy, radiotherapy, and molecular targeted agents, as they can modulate the tumour microenvironment, increase tumour immunogenicity, and overcome therapeutic resistance.

Ongoing biomarker-driven clinical trials continue to evaluate the safety, efficacy, and optimal combination of epigenetic agents with existing treatment modalities. As the understanding of epigenetic regulation continues to evolve, epigenetic modification therapy is expected to become an integral component of personalized treatment strategies for patients with head and neck cancers [63].

Figure 2 illustrates the significant role of oncogenes in the initiation and progression of head and neck cancer. Genetic alterations in key oncogenes such as EGFR, MYC, and RAS lead to uncontrolled cellular proliferation, enhanced tumor growth, and increased potential for invasion and metastasis. These changes also contribute to the development of resistance to conventional therapies, ultimately affecting patient survival and prognosis. The figure emphasizes how activation of oncogenic pathways drives major cancer hallmarks, including tumor expansion and therapeutic resistance. By targeting these specific molecular pathways, modern treatment strategies aim to inhibit oncogene activity. Such targeted approaches can help control tumor progression and improve overall clinical outcomes [43].

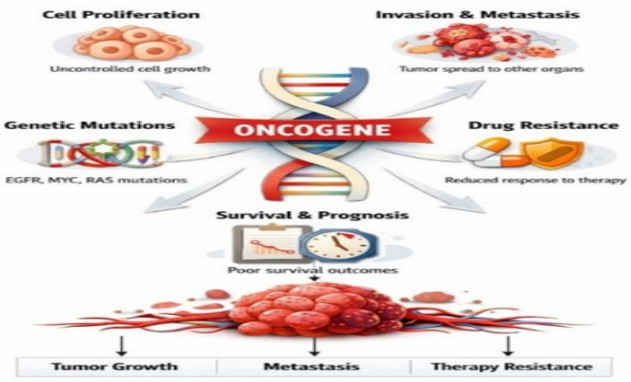


Figure 2: Role of oncogenes in the initiation and progression of head and neck cancer

## Resistance Mechanisms to Precision Therapies

Despite remarkable advances in precision oncology, therapeutic resistance remains one of the great-

est challenges in the management of head and neck squamous cell carcinoma (HNSCC). Although targeted therapies directed against molecular drivers such as EGFR, MYC, and RAS have improved clinical outcomes in selected patient populations, many individuals either fail to respond to treatment (intrinsic resistance) or develop disease progression after an initial period of response (acquired resistance). These resistance mechanisms arise from a complex interplay of genetic, epigenetic, cellular, and microenvironmental factors that ultimately limit the long-term effectiveness of precision-based therapies [46].

One of the primary mechanisms of resistance involves alterations within the EGFR signalling pathway. Secondary mutations, receptor amplification, increased ligand production, and activation of alternative receptor tyrosine kinases can restore downstream signalling despite EGFR inhibition [47]. In addition, compensatory activation of the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways enables tumour cells to maintain proliferation, survival, and metastatic potential even in the presence of targeted agents. Such bypass signalling mechanisms reduce the therapeutic efficacy of EGFR-directed monoclonal antibodies and tyrosine kinase inhibitors, necessitating the development of combination treatment strategies [48].

The MYC oncogene also contributes significantly to therapeutic resistance through its ability to regulate genes involved in cell cycle progression, DNA repair, metabolic reprogramming, and apoptosis. Persistent MYC activation promotes tumour cell survival under therapeutic stress, allowing malignant cells to evade treatment-induced cell death [49]. Furthermore, MYC-mediated metabolic adaptation enhances cellular resilience, enabling cancer cells to survive in hypoxic and nutrient-deprived tumour microenvironments. These biological properties have made MYC an attractive yet challenging therapeutic target, as direct inhibition remains technically difficult [50].

Similarly, aberrant activation of the RAS signalling pathway, particularly involving HRAS, promotes resistance by continuously stimulating downstream proliferative and survival pathways independent of receptor inhibition. RAS-driven tumours frequently exhibit enhanced invasive capacity, increased metastatic behaviour, and reduced sensitivity to chemotherapy, radiotherapy, and targeted therapies [51]. Consequently, current research focuses on inhibiting downstream signalling molecules, including MEK, ERK, and PI3K, as well as evaluating novel combination approaches to suppress compensatory pathway activation [52].

Another major contributor to therapeutic failure is tumour heterogeneity. Head and neck cancers display substantial genetic diversity both between patients (interpatient heterogeneity) and within individual tumours (intratumoral heterogeneity). Different tumour cell populations may harbour distinct molecular alterations, resulting in variable sensitivity to targeted agents [53]. Under therapeutic pressure, resistant cellular clones can undergo clonal selection and expansion, eventually leading to disease recurrence and progression. This dynamic genomic evolution highlights the importance of repeated molecular profiling during treatment.

The tumour microenvironment further influences resistance by creating an immunosuppressive milieu characterized by regulatory T cells, tumour-associated macrophages, cancer-associated fibroblasts, hypoxia, and inflammatory cytokines. These

components promote tumour survival, impair anti-tumour immune responses, and reduce the effectiveness of both immunotherapy and targeted therapy [54]. Moreover, epigenetic alterations, including abnormal DNA methylation, histone modifications, and dysregulated non-coding RNAs, can alter gene expression without changing the DNA sequence, facilitating adaptive resistance and continued tumour progression.

To overcome this resistance, precision oncology in the United States is increasingly adopting comprehensive genomic profiling, liquid biopsy, biomarker-guided therapy selection, and rational combination treatment strategies integrating targeted therapy, immunotherapy, radiotherapy, and epigenetic agents [55]. Advances in next-generation sequencing, artificial intelligence-assisted molecular analysis, and real-time monitoring of circulating tumour DNA are enabling earlier identification of resistance mechanisms and more personalized therapeutic interventions. Continued research into the molecular interactions among EGFR, MYC, and RAS, together with the discovery of novel predictive biomarkers and resistance pathways, will be essential for developing durable precision therapies and improving long-term survival outcomes for patients with head and neck cancers [56].

## Precision Clinical Trials in the United States

Precision clinical trials have become a cornerstone of advancing personalized cancer care in the United States by evaluating therapies based on the molecular characteristics of individual tumors rather than solely on their anatomical origin [64]. In head and neck squamous cell carcinoma (HNSCC), these innovative trial designs have accelerated the development of targeted therapies directed against molecular alterations involving **EGFR, MYC, and RAS**, thereby improving patient selection and treatment outcomes [57]. **Basket trials** enroll patients with different cancer types that share a common genomic alteration, enabling the assessment of targeted therapies across multiple malignancies with similar molecular profiles. In contrast, **umbrella trials** focus on a single cancer type, such as HNSCC, while assigning patients to different therapeutic arms based on distinct molecular biomarkers identified through comprehensive genomic profiling [58].

One of the most influential precision oncology initiatives is the **NCI-Molecular Analysis for Therapy Choice (NCI-MATCH)** trial, which matches patients with targeted therapies according to actionable genetic alterations irrespective of tumor histology. This landmark study has demonstrated the feasibility of biomarker-driven treatment selection and has significantly contributed to the expansion of precision medicine in oncology [59]. Similarly, numerous **precision oncology trials** are investigating novel inhibitors targeting EGFR signalling, downstream RAS-associated pathways, MYC -regulated transcription, and combination regimens integrating immunotherapy, radiotherapy, and molecular targeted agents [60].

Furthermore, **biomarker-driven studies** utilize genomic, transcriptomic, and proteomic analyses to identify predictive biomarkers that guide individualized therapeutic decisions and monitor treatment response [61]. **Adaptive trial designs** further enhance clinical research by allowing protocol modifications based on interim efficacy and safety data, thereby improving trial efficiency and accelerating the evaluation of promising therapies. Collectively, these innovative clinical trial strategies are transforming precision oncology in the United States,

facilitating the translation of molecular discoveries into personalized treatment approaches and improving outcomes for patients with head and neck cancers [62].

## Challenges in Precision Oncology

Although precision oncology has evolved considerably over the past decade, several challenges continue to limit its widespread implementation in the management of head and neck cancers. Drug resistance, arising from secondary genetic alterations, activation of alternative signalling pathways, and adaptive tumour evolution, often reduces the long-term efficacy of targeted therapies directed against EGFR, MYC, and RAS [36]. Furthermore, interpatient and intratumoral heterogeneity contributes to variable therapeutic responses and complicates treatment selection. The clinical application of comprehensive genomic profiling is also hindered by genomic complexity, as many detected alterations remain non-actionable or of uncertain clinical significance. Additional barriers include the limited availability of validated molecular biomarkers, which restrict accurate patient stratification and prediction of treatment response [37]. The high cost of genomic testing, targeted therapies, and advanced molecular diagnostics, coupled with disparities in healthcare access, limits the availability of precision medicine across diverse populations in the United States. Moreover, integrating genomic data into routine clinical practice requires multidisciplinary expertise, standardized testing protocols, and robust bioinformatics infrastructure. Ethical considerations, including patient privacy, informed consent, genetic data security, and equitable access to precision-based therapies, must also be addressed [31]. Overcoming these challenges is essential to maximize the clinical benefits of personalized oncology and improve outcomes for patients with head and neck cancers.

## Future Perspectives

The future of precision oncology in head and neck cancers lies in the integration of emerging technologies that enable increasingly personalized treatment strategies. **Multi-omics** approaches combining genomics, transcriptomics, proteomics, and metabolomics, together with **spatial transcriptomics** and **single-cell sequencing**, will provide a comprehensive understanding of tumour heterogeneity and the tumour microenvironment [36]. Innovative technologies such as **CRISPR-based gene editing**, **AI-guided therapeutic decision-making**, and **digital twin** models are expected to facilitate precise target identification and individualized treatment planning [41]. Furthermore, advances in **nanomedicine**, **personalized cancer vaccines**, and **combination targeted therapies** integrating EGFR, MYC, and RAS-directed approaches with immunotherapy and radiotherapy hold significant promise for overcoming therapeutic resistance, improving clinical outcomes, and advancing precision oncology for patients with head and neck cancers in the United States [42].

## Conclusion

The present review highlights the pivotal contribution of EGFR, MYC, and RAS alterations in driving the initiation, progression, and therapeutic resistance of head and neck cancers. Their intricate molecular interactions underscore the complexity of tumor biology and the need for precise diagnostic and prognostic markers. Advancements in targeted and molecular-based therapies offer promising avenues for improved disease management and personalized treatment strategies. Continued research focusing on these oncogenic pathways is essential to enhance clinical outcomes and develop

more effective, patient-specific interventions.

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