

Review

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Review

Progress in Precision Medicine for Head and Neck Cancer

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Simple Summary: Head and neck squamous cell carcinoma (HNSCC) is a deadly form of cancer affecting areas like the mouth, throat, and larynx. This review explores the complex molecular pathways involved in HNSCC development and progression, focusing on the role of microRNAs (miRNAs) - small molecules that regulate gene expression. We aim to provide a comprehensive overview of how miRNAs influence HNSCC, their potential as diagnostic and prognostic markers, and their use in developing new targeted therapies. We also discuss promising nanotechnology-based approaches for delivering miRNA therapies more effectively. By synthesizing current knowledge on miRNAs in HNSCC, this research may help identify new biomarkers for early detection and prognosis, as well as novel therapeutic targets. Ultimately, these insights could lead to improved personalized treatments and better outcomes for HNSCC patients.

Abstract: This paper presents a comprehensive comparative analysis of head and neck cancer (HNC) biomarkers, a prevalent but molecularly diverse malignancy. We detail the roles of key proteins and genes in tumorigenesis and progression, emphasizing their diagnostic, prognostic, and therapeutic relevance. Our bioinformatic validation reveals crucial genes such as AURKA, HMGA2, MMP1, PLAU, and SERPINE1, along with microRNAs (miRNA) linked to HNC progression. OncomiRs, including hsa-miR-21-5p, hsa-miR-31-5p, hsa-miR-221-3p, hsa-miR-222-3p, hsa-miR-196a-5p, and hsa-miR-200c-3p, drive tumorigenesis, while tumour-suppressive miRNAs like hsa-miR-375 and hsa-miR-145-5p inhibit it. Notably, hsa-miR-155-3p correlates with survival outcomes in addition to genes RAI14, S1PR5, OSBPL10, and METTL6, highlighting its prognostic potential. Future directions focus on leveraging precision medicine, novel therapeutics, and AI integration to advance personalized treatment strategies to optimize patient outcomes in HNC care.

Keywords: precision medicine; biomarkers; genetic alterations; head and neck cancer; targeted therapy

1. Introduction

Head and neck cancer (HNC) is often associated with a malignancy that can be successfully treated, however it still represents a substantial global health challenge due to its high prevalence

within society and its significant symptoms. Considering the distinct molecular characteristics of HNC, it is a prime subject for a comparative review. HNC ranks among the top ten cancers globally, affecting critical functions such as speech and swallowing [1]. This cancer's diverse molecular basis and clinical manifestations necessitate a comprehensive understanding at both molecular and clinical levels to help identify unique and shared pathways, allowing for improved diagnosis and clinical management through the development of targeted therapies. Through examination of this cancer potential innovations in treatment strategies, advanced personalized medicine, and improved patient outcomes can be emphasized [2,3].

The global burden of HNC is significant due to its profound impact on mortality and morbidity as essential functions such as breathing, eating, and speaking are impaired. However, the prevalence and outcomes of HNC vary significantly from region to region, influenced by differences in exposure, risk factors, and access to healthcare services [4,5].

HNC is significantly influenced by genetic predispositions and environmental factors, sharing common risk factors such as age and family history [6–8]. Susceptibility increases with age, and family history may indicate a genetic link that elevates risk [9]. With an aging global population, the incidence and mortality rates of both cancers are expected to rise. Symptoms commonly appear in advanced stages, complicating optimal cancer treatment and significantly reducing survival rates. This highlights the need for regular screening, heightened awareness, especially for high-risk groups, and the discovery of novel biomarkers to improve both treatment strategies and cure rates. Addressing these challenges requires comprehensive strategies, including prevention, early detection, and tailored treatments [3,10]. (Figure 1)

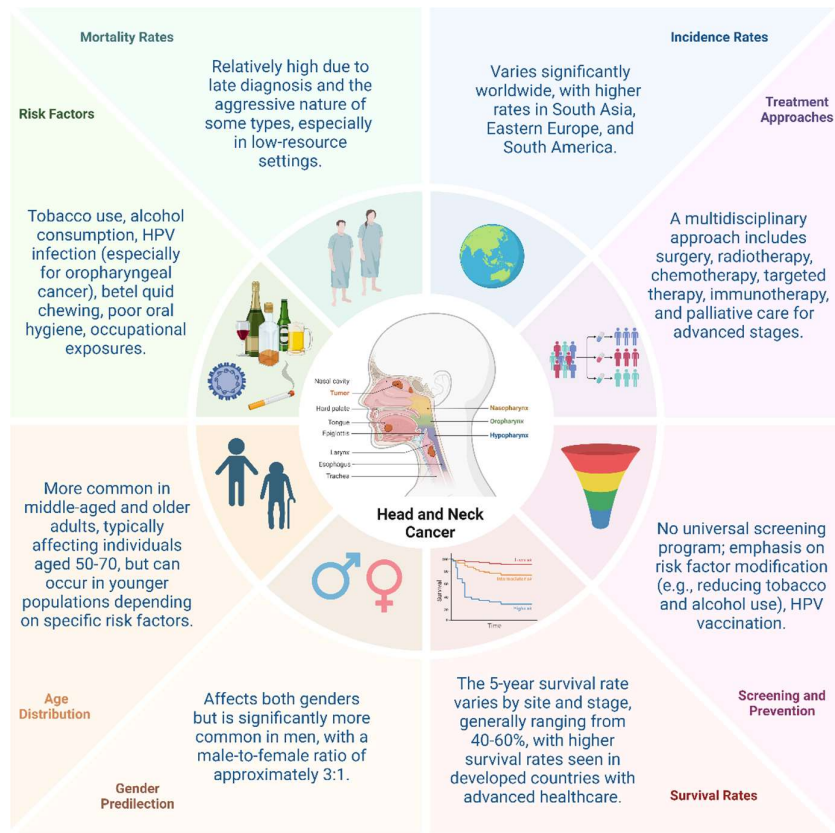


Figure 1. Epidemiological Aspect of Head and Neck Cancer (Created with BioRender.com).

1.1. The Importance of Molecular Studies in Understanding Head and Neck Cancer

Molecular studies have revolutionized our understanding of HNC, revealing the intricate genetic and molecular landscapes underlying this disease. In HNC, molecular research has shown the central role of viral aetiologies, particularly human papillomavirus (HPV) and Epstein-Barr virus (EBV), in the pathogenesis of these cancers. HPV-positive oropharyngeal cancers, for example, are

now recognized as distinct cancers with an improved prognosis and response to treatment compared to HPV-negative cancers. The identification of these viral markers has facilitated the development of targeted therapies and preventive vaccines, such as the HPV vaccine, which has the potential to reduce the incidence of these cancers significantly [11,12].

Molecular profiling of HNC has identified key genetic alterations, including mutations in TP53, NOTCH1, and PIK3CA and amplifications in oncogenes like epidermal growth factor receptor (EGFR). These findings have led to targeted therapies, such as EGFR inhibitors, tailored to each patient's tumour. Understanding HNC molecular pathways has improved patient stratification for personalized treatment, enhancing outcomes and reducing toxicity [13,14]. The insights gained from molecular studies have not only deepened the understanding regarding HNC biology but have also revolutionized the clinical treatment of this condition. By identifying critical genetic and molecular alterations, researchers and clinicians can improve diagnostic accuracy and personalize medicine plans based on more effective, targeted therapies, thus improving treatment outcomes. Among the essential regulators of molecular profiling in head and neck cancer, microRNAs have emerged as pivotal component, influencing gene expression and contributing to the complexity of tumour biology.

1.2. Introduction to miRNAs in Head and Neck Cancer

MicroRNAs (miRNAs) are small (18-25 nucleotides), non-coding RNA molecules that regulate gene expression post-transcriptionally. They are pivotal in various biological processes, including cell proliferation, apoptosis, metastasis, and response to therapy. In addition, the mutual characteristics of oncogenes or tumour suppressors make them invaluable for understanding cancer biology. Their potential as biomarkers for early diagnosis, prognosis, and therapeutic targets highlights their importance in precision medicine. In HNC, miRNAs have emerged as crucial regulators, influencing the molecular landscape, and provides biomarkers as potential targets for diagnosis, prognosis, and therapeutic intervention. Despite advances in treatment, the prognosis for HNC patients remains challenging due to late-stage diagnosis, high recurrence rates, and the development of resistance to conventional therapies [15]. Emphasizing the crucial role of miRNAs in cancer biology presents promising targets for therapeutic intervention. This section provides a comprehensive overview of miRNAs' roles in HNC, underscoring their significance in advancing personalized medicine and improving patient outcomes.

1.3. Introduction to miRNAs in Head and Neck Cancer

Improving diagnostic procedures for HNC involves the study of complex and varied pathways. The route to improving diagnostic procedures for HNC is challenging. For HNC, diagnosis primarily relies on physical examinations as there are no efficient and standardized screening methods, often resulting in late detection when the cancer is more advanced and difficult to treat. These diagnostic limitations have driven the research and substantiation of new biomarkers for increased accuracy and less invasive diagnostic alternatives for cancer. Understanding the molecular intersections of HNC is critical for developing personalized treatment approaches and improving patient outcomes. This review addresses the intricate details of these cancers, highlighting their global prevalence, significance, and the central role of molecular studies in deciphering their complex genetic foundation.

Key risk factors for HNC include tobacco use, alcohol consumption, and infections with oncogenic viruses such as HPV and EBV [16–18]. Molecular profiling has identified various genetic alterations, including mutations in tumour suppressor genes such as TP53 and PIK3CA and amplifications in oncogenes such as EGFR. These discoveries have facilitated the development of targeted therapies and improved patient stratification and treatment outcomes [11,12]. Understanding these molecular attributes are critical for developing targeted therapies and improving the precision of treatment strategies [14,19], which are expected to improve patient outcomes in HNC significantly. In HNC, the identification of viral aetiologies and genetic alterations has paved the way for targeted therapies and preventive measures such as the HPV vaccine, which has the potential to reduce cancer incidences significantly (**Table 1**).

Table 1. Molecular Subtypes of Head and Neck Cancer: Characteristics and Clinical Implications.

Molecular Subtype	Characteristic Features	Clinical Implications	References
HPV-positive	Presence of HPV DNA, overexpression of p16, and absence of TP53 mutations.	Better response to treatment and prognosis compared to HPV-negative tumours.	[20]
Basal	High expression of basal cell markers, EGFR amplification, and TP53 mutations.	Poor differentiation and worse prognosis.	[21]
Mesenchymal	Features of epithelial-to-mesenchymal transition, expression of mesenchymal markers.	Resistance to chemotherapy and radiation therapy.	[22]
Atypical	Mutations in NOTCH1, low HPV, and p16 expression.	Diverse prognosis, potential sensitivity to NOTCH inhibitors.	[23]
Classical	High expression of genes involved in cell cycle regulation, notably cyclin D1 and CDK6.	Aggressive behaviour, potential targets for cell cycle inhibitors.	[24]
Immune-Related	High infiltration of immune cells and expression of immune checkpoint molecules such as PD-L1.	Potential responsiveness to immunotherapy, particularly immune checkpoint inhibitors.	[25]
Hypoxic	Overexpression of hypoxia-inducible factors (HIFs), adaptation to low oxygen environments.	Poor prognosis, potential targets for therapies aimed at hypoxic conditions.	[26]
Metabolic	Alterations in metabolic pathways, increased glycolysis (Warburg effect), overexpression of GLUT1.	Potential for targeting metabolic pathways, implications for metabolic inhibitors.	[27]

2. Signature Protein/Gene in Head and Neck Cancer

2.1. Literature-Driven Insights

The importance of identifying the pivotal proteins and genes involved in this malignancy has become increasingly apparent to acquiring a greater understanding of HNC. In HNC, human papillomavirus (HPV) oncoproteins E6 and E7 play a crucial role, particularly in oropharyngeal carcinoma, by inactivating the tumour suppressor proteins p53 and retinoblastoma (Rb), respectively [11,12]. In addition, mutations in TP53, CDKN2A, and PIK3CA and amplifications in EGFR are common in HNC and drive tumorigenesis via different pathways.

Several other proteins also play a crucial role in the progression of HNC. Tissue inhibitors of metalloproteinases (TIMPs) are significantly involved in the regulation of extracellular matrix (ECM) remodelling and metastasis through their inhibitory effect on matrix metalloproteinases (MMPs) and

thus play a crucial role in the tumour microenvironment [28]. Similarly, galectin-3 (Gal-3) is involved in various aspects of cancer progression, including proliferation, angiogenesis, metastasis, and immune evasion [29].

In head and neck cancer, MMP25 expression correlates with prognosis and degree of immune infiltration, particularly with CD4+ memory T cells, and is involved in oncogenic signalling pathways such as p53 signalling and PI3K/AKT/mTOR signalling. This suggests its crucial role in cancer progression and immune responses [30]. Fibronectin 1 (FN1) is significantly overexpressed in head and neck squamous cell carcinoma (HNSCC) and correlates with higher pathologic stages and poor prognosis. Its downregulation suppresses the proliferation, migration, and invasion of HNSCC cells and inhibits M2 polarization of macrophages in vitro, suggesting its role in promoting HNSCC progression and immune modulation [31]. This indicates the role of fibronectin in modulating post-transcriptional changes that lead to cancer progression [32].

TIMPs, Gal-3, MMPs, and fibronectin are integral to the dynamics of the tumour microenvironment in both head and neck cancer, influencing tumour growth, metastasis, and immune responses. These molecules can potentially serve as biomarkers for diagnosis, prognosis and targets for therapeutic intervention. Understanding their role and interactions is essential for developing personalized treatment approaches and improving treatment outcomes for this cancer (Table 2).

Table 2. Key Proteins and Genes in Head and Neck (HNC).

Key Protein/Gene	Role in Cancer	Clinical Relevance	Ref
HPV E6/E7	Oncogenic viral proteins that inactivate p53 and Rb, promoting cell cycle progression.	HPV status is a critical prognostic marker and determines treatment strategies.	[33]
EGFR	Overexpressed in many HNCs, leading to increased cell proliferation.	Targeted by EGFR inhibitors like cetuximab, it predicts responsiveness to therapy.	[34]
TP53	Mutations lead to loss of tumour suppressor function, contributing to carcinogenesis.	Associated with poor prognosis and aggressive disease; potential target for therapy.	[35]
CDKN2A (p16)	Tumour suppressor gene, loss contributes to cell cycle deregulation.	Frequently mutated or deleted in HNC, indicative of poor prognosis.	[36]
PIK3CA	Mutation activates the PI3K/AKT pathway, promoting tumorigenesis.	Target for PI3K inhibitors associated with therapeutic resistance.	[37]
TIMPs (Tissue Inhibitors of Metalloproteinases)	Regulate ECM remodelling and metastasis by inhibiting MMPs,	Targets for therapy and markers for	[38]

	potentially suppressing tumour progression.	disease progression and response to treatment.	
Gal-3 (Galectin-3)	Involved in cell adhesion, migration, and tumour progression.	Potential marker for prognosis and therapeutic targeting.	[39]
MMPs (Matrix Metalloproteinases)	Facilitate tumour invasion and metastasis through ECM degradation.	Biomarkers for invasive potential and therapeutic targets.	[40]
Fibronectin	Contributes to cell adhesion and migration, influencing tumour growth and metastasis.	Insights into tumour progression and potential therapeutic implications.	[41]

2.2. Database-Driven Insights

To identify datasets from HNC, a dataset search was performed in the Genome Expression Omnibus (GEO). These datasets contain gene expression data for HNC (GSE227919; GSE142083; GSE138206; GSE130605). The most significant differentially expressed genes (DEGs) were identified for HNC cancer. Further analysis identified 37 potential biomarkers for HNC, of which the top 5 DEGs were highlighted. In HNC, the most upregulated genes are MMP1 (matrix metalloproteinase 1), SERPINE1 (serpin family E member 1), PLAU (urokinase-type plasminogen activator), AURKA (Aurora kinase A), and HMGA2 (high mobility group AT-hook 2). Therefore, these genes may serve as biomarkers to distinguish patients with HNC from those without this cancer. This conclusion is supported by literature data from previous studies (Table 3).

Table 3. Characterization of Top DEGs Identified for HNC.

Gene	Role in Cancer Identified in Previous Studies	Reference
AURKA	High expression is associated with cancer progression, dysregulated proliferation, and inhibition of apoptosis. It is a good predictor of OS, with overexpression representing a poor prognosis.	[42–44]
HMGA2	Overexpression increases tumour cell proliferation, migration, invasion, and metastasis. A good predictor of OS, with high levels indicating poor prognosis.	[45–47]
MMP1	Upregulation is associated with ECM degradation and consequent cancer-promoting invasiveness. Its expression correlates with T stage (TNM classification) and cancer progression.	[48,49]
PLAU	Overexpression is associated with ECM degradation, an increased risk of developing HNC, and an upregulation of MMP1. Knockdown inhibits proliferation, invasion, and metastasis.	[49,50]
SERPINE1	Overexpression is associated with N stage (TNM classification), poor DFS, and the promotion of radiotherapy resistance. Inhibition leads to decreased cell proliferation and invasion.	[4,51,52]

In HNC, the molecular profile is dominated by critical proteins and genes that drive tumorigenesis, impact patient prognosis, and serve as targets for therapy. AURKA, a member of the

Aurora serine/threonine kinase family, plays a role in maintaining chromosome stability and is expressed in many tissues. It is overexpressed in various tumours, including glioblastoma, cervical cancer, and HNC [42,43]. AURKA has been identified as a novel therapeutic target and predictor of overall survival (OS) in HNC [44]. High expression levels of AURKA are associated with the progression of HNC and poor prognosis, especially in HPV-negative tumours. However, AURKA is also known to be upregulated by HPV E7, which increases tumour cell proliferation. Overexpression of AURKA inhibits apoptosis by phosphorylating p73, a protein related to programmed cell death [43]. HMGA2, which belongs to the high mobility group AT-hook (HMGA) gene family, encodes a protein that regulates gene expression, cell replication, and repair. HMGA2 has been identified as an oncogene associated with cancer development when expressed at high levels [45]. Overexpression of HMGA2 is associated with processes related to the progression of HNC, such as significant invasiveness, metastasis, epithelial-mesenchymal transition, dysregulated proliferation and migration of tumour cells [45,46]. The expression of HMGA2 influences OS in HNC, with a high expression indicating a poor prognosis [46,47]. MMP1, a member of the matrix metalloproteinase family, is involved in extracellular matrix (ECM) degradation by cleaving collagen IV and gelatine [48]. MMP1 is overexpressed in HNC, and its expression correlates with T-stage (TNM classification) and cancer progression through tumour-promoting invasion [49]. PLAU, which belongs to the S1 serine peptidase of the plasminogen activator family, encodes a secreted serine protease that converts plasminogen to plasmin [49,50]. This enzyme promotes ECM degradation and facilitates tumour cell invasion and metastasis. In HNC samples, PLAU expression is upregulated and is associated with lower overall survival, poor disease-free survival, and an increased risk of developing HNC [49]. Overexpression of PLAU also leads to upregulation of MMP1. Suppression of PLAU inhibits HNC cells' proliferation, migration, and invasion capacities, while its overexpression has the opposite effect [49]. SERPINE1, a serine protease inhibitor family member, is overexpressed in HNC samples [51,52]. Overexpression of SERPINE1 is associated with the N-stage (TNM classification) and may play a role in tumour angiogenesis and metastasis. Its inhibition is associated with reduced cell proliferation and invasion [53]. SERPINE1 is also a potential prognostic biomarker, as its expression correlates with disease-free survival (DFS) in HNC [52]. Overexpression of SERPINE1 promotes resistance to radiotherapy in HNC patients [51]. These essential proteins and genes play crucial roles in the development and progression of HNC and serve as potential biomarkers for diagnosis, prognosis, and targets for therapeutic intervention. Thus, understanding their functions and interactions is essential for developing personalized treatment approaches and improving treatment outcomes in these cancers.

3. Molecular Pathways Involved in Head and Neck Cancer

As with the genetic landscape, the molecular profiles of HNC have unique features. Dysregulation of signalling pathways such as the EGFR, PI3K/AKT, and RAS-RAF-MEK pathways is critical in HNC, affecting cell cycle regulation, cellular metabolism, and apoptosis. In addition, in oropharyngeal carcinoma, HPV adds a unique viral mechanism to tumour development, mainly through the viral oncoproteins E6 and E7, which affect tumour suppressor pathways such as p53 and Rb [14,54].

Functional enrichment analysis was performed on the string platform using the DEGs identified for HNC (n=37). This analysis aimed to assess the functions of these genes and their association with HNC. The DEGs identified for HNC were associated with the cancer and several signalling pathways and molecular functions related to cancer development and progression, including ERBB and TGF- β signalling, ECM degradation, and focal adhesion. In addition, these genes have been linked to other diseases, such as gastrointestinal and pancreatic cancer and cardiovascular disorders, where they have been found expressed in tissues of the cardiovascular system. ERBB signalling includes elements of the HER family: HER1 (EGFR), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4) [55–57]. EGFR plays an important role in signalling pathways critical to cancer progression, including Ras/Raf/MEK/ERK and PI3K/AKT/mTOR. In HNC, studies indicate that EGFR mutations significantly impact prognosis more than TP53 mutations [57,58]. Other HER family members are also involved in developing HNC and show upregulated expression in patients [57,59]. TGF- β signalling regulates epithelial-to-mesenchymal transition as well as cell differentiation and

proliferation in HNC. It plays a dual role by inhibiting dysregulated cell proliferation at early stages while promoting invasion and metastasis at later stages [60].

The ECM is essential for physical interactions with cancer cells and serves as a reservoir for various ligands and growth factors that influence the tumour microenvironment. During cancer progression, focal adhesion is lost, which decreases cellular adhesion and allows cancer cells to permeate the ECM, altering its composition and organization, ultimately leading to degradation. This process is promoted by increased MMP expression in cancer [61]. After degradation of the ECM, the cancer cells enter the bloodstream, invade other tissues and metastasize [62].

As mentioned, HNC shares alterations in the PI3K/AKT/mTOR signalling pathway, highlighting its universal role in cancer progression. Targeted therapies in cancers aim to inhibit this pathway to slow tumour growth and reduce tumour survival [63]. In HNC, targeted agents against EGFR, such as cetuximab, have shown clinical benefits by exploiting abnormal activation of growth factor signalling pathways [4].

Unique to HNC is the influence of viral oncogenes in HPV-associated cancers, necessitating therapeutic strategies that target viral proteins or their effects on cellular mechanisms. Immunotherapy that harnesses the immune system's ability to recognize and destroy cancer cells has shown promise in HNC, particularly PD-1/PD-L1 inhibitors such as Pembrolizumab and Nivolumab [64]. The distinct molecular pathology of HNC emphasizes the need for cancer-specific targeted therapies that reflect their unique molecular basis [65]. Understanding these pathways helps in the development of targeted therapies and the identification of potential biomarkers for better disease management [64,65].

4. Role of Biomarkers in Head and Neck Cancer

Biomarkers are crucial for offering insights into the molecular basis of the disease and providing valuable diagnostic and prognostic information for HNC. Notable biomarkers include DNA methylation patterns, circulating microRNAs, and proteins such as EGFR and HPV oncoproteins (E6 and E7). These markers help detect and assess the cancer's aggressiveness at an early stage, enabling customized therapeutic measures [66–68]. Extensive studies have indicated the significant clinical potential of these biomarkers in HNC. Emerging biomarkers, including gene expression profiling in HNC, represent the next frontier in cancer diagnostics [69,70]. These novel biomarkers promise to improve the accuracy of cancer detection, prognosis, and monitoring, and additionally has the potential to revolutionize personalized medicine in oncology. Integrating biomarker testing into clinical practice is expected to significantly improve patient outcomes by enabling earlier detection, more accurate identification of disease stage, and design of optimal personalized therapeutic strategy based on individual tumour characteristics. As part of the collective effort to improve and extend the use of biomarkers in cancer detection and treatment e.g., Filippini et al. (2023) [71] present a systematic review of current data on diagnostic and prognostic molecular biomarkers for head and neck cancer of unknown primary (HNCUP). Using an electronic database and following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, they identified 704 articles, of which 23 studies were carefully selected for inclusion. Fourteen studies focused on diagnostic biomarkers for HNCUP, with an emphasis on HPV and EBV, as these are significantly associated with oropharyngeal and nasopharyngeal cancers, respectively [71].

The review underlines the prognostic importance of HPV, which is associated with improved disease-free treatment outcomes and overall survival rates. Currently, HPV and EBV are the only biomarkers for HNCUP used in the clinical setting. Improving molecular characterization and developing accurate tissue of origin classifiers are crucial to advance the diagnosis, accurate identification of disease stage, and treatment of HNCUP patients [71]. The ongoing development and validation of new biomarkers is imperative to improve the precision of cancer treatment, minimize overdiagnosis and overtreatment, and ultimately improve patient survival and quality of life (Table 4).

Table 4. Diagnostic and Prognostic Biomarkers in HNC: Effectiveness Overview.

Biomarker	Diagnostic Use	Prognostic Use	Potential Effectiveness	Ref
HPV DNA	Identifies HPV-associated HNC	Indicates better prognosis and response to treatment in HPV-positive cases	Highly effective for subclassification and prognosis	[72]
EGFR	Used for identifying tumours with EGFR overexpression	Associated with poor response to radiation and certain chemotherapies	Effective in selecting candidates for EGFR-targeted therapies	[73]
p16	Surrogate marker for HPV oncogenic activity	Suggests improved outcomes in HPV-positive HNC	Widely used, offers good prognostic value	[74]

5. Functional Roles of miRNAs in Head and Neck Cancer

Many research studies have investigated miRNAs' role in HNC. Several miRNAs have been identified as crucial regulators of pathways critical to the pathogenesis of HNC. This review examines recent findings in miRNA studies of HNC and will be discussed based on their role as oncomiR and tumour suppressors.

5.1. OncomiRs in Head and Neck Cancer

As indicated, oncomiRs contribute to cancer progress by targeting tumour suppressor genes. In HNC, several oncomiRs have been identified in tumorigenesis, metastasis, and resistance to therapy [75]. MiR-21 is the first and the most studied oncomiRs in HNC. It is frequently overexpressed in HNC [76,77]. MiR-21 targets tumour suppressor genes such as PTEN/AKT, TPM1, and PDCD4 pathways in HNC [78,79]. Overexpression of miR-21 promotes cell proliferation, invasion, and resistance to apoptosis in HNC [75]. Another oncomiR involved in HNC is miR-155, which targets several genes in cell cycle regulation and apoptosis [80]. For example, the suppressor of cytokine signalling 1 (SOCS1) is one of the targetable genes that negatively regulates the JAK/STAT pathway [81]. MiR-155 elevation downregulates SOCS1 expression, increasing cell growth and cell survival, making it a potential marker for aggressive HNC [82]. Targeting miR-155 expression and overexpression of SOCS1 has a potent antitumor effect on HNC [83,84]. MiR-31 is also upregulated in HNC and plays a significant role in cancer progression, specifically in oral squamous cell carcinoma (OSCC) through regulation of gene expression, cell proliferation, cell cycle regulation, cell survival, signal transduction, and epithelial mesenchyme transition. In OSCC it targets genes such as FIH (factor-inhibiting HIF) and LATS2 (large tumour suppressor kinase 2), involved in hypoxia response and the Hippo signalling pathway, respectively [85]. MiR-31 upregulation contributes to proliferation, invasion, and angiogenesis, leading to more aggressive tumour behaviour in HNC [86]. Another group of miRNAs involved in HNC oncogenesis is the miR-221/222 cluster. These miRNAs target the cyclin-dependent kinase inhibitor p27Kip1 and the pro-apoptotic protein BMF [87]. MiR-221/222 upregulation increases cell cycle progression, reduces apoptosis, and enhances resistance to chemotherapy [88,89]. Ultimately, miR-196a is also overexpressed in HNC and promotes tumour progression, cell proliferation, migration, and invasion, leading to poor prognosis Oncogenic miR-196a directly targets annexin A1 (ANXA1), a gene involved in cell differentiation and apoptosis. ANXA1 protein and mRNA were found to be downregulated in HNC tissues. However, miR-196a functional contribution to HNC development has remained unclear [90]. OncomiRs potentially serve

as biomarkers for early detection, prognosis, and monitoring treatment response in HNC [91]. OncomiRs can be targeted by antagomirs (anti-miRNAs) [92] or miRNA sponges to inhibit their oncogenic effects [93]. Clinical trials are exploring the efficacy of such approaches in various cancers, including HNC [94].

5.2. Tumor-Suppressive miRNAs in Head and Neck Cancer

As outlined earlier, tumour-suppressive miRNAs inhibit cancer development and progression by targeting oncogenes and other genes involved in cell proliferation, invasion, and survival. In HNC, several tumour-suppressive miRNAs have been identified, playing crucial roles in maintaining cellular homeostasis and preventing malignant transformation. Through analysis of recent findings, the key tumour-suppressive miRNAs in HNC have been documented. MiR-34a is a well-known tumour suppressor miRNA involved in various cancers, including HNC. It targets multiple oncogenes, such as BCL2, MET, and CDK6. MiR-34a induces apoptosis, inhibits cell proliferation, and suppresses metastasis. MiR-34a is considered a novel and highly sensitive biomarker for HNSCC diagnostic applications [75]. MiR-200c is a part of the miR-200 family, known for its role in epithelial-mesenchymal transition (EMT). It was demonstrated that miR-200c expression is significantly downregulated in OSCC tissues compared with adjacent non-tumour tissues, suggesting that miR-200c might be a potential prognostic biomarker for OSCC [95]. It inhibits ZEB1 and ZEB2, transcription factors that promote EMT and metastasis, thereby reducing invasion and metastasis [96]. MiR-200c-3p is another member of the miR-200 family shown to have a significantly downregulated expression in HNC tissues. In HNC cells, ectopic miR-200c-3p expression inhibits viability, clonogenicity, migration, and invasion [97]. Additionally, miR-375 is highly downregulated in HNC and functions as a tumour suppressor. It targets genes involved in cell cycle regulation, such as insulin-like growth factor 1 receptor (IGF-1R). MiR-375 upregulation inhibits growth and induces cell cycle arrest in G0/G1 phase significantly. It enhances apoptosis and radiosensitivity in HNC [98]. Reduced levels of miR-375 are associated with aggressive tumour behaviour and poor clinical outcomes [99]. MiR-145 is another tumour-suppressive miRNA that is significantly downregulated in HNC. MiR-145 is involved in the p53 signalling pathway. Downregulation of miR-145-5p oncogenes like FSCN1 (fascin actin-bundling protein 1) protein level or SOX2, causing migration, invasion, tumour growth and EMT. Its minimal expression is correlated with advanced disease stages and poor survival rates [80]. Tumour-suppressive miRNAs can serve as biomarkers for early detection, prognosis, and monitoring response to HNC therapy. It could inhibit tumour growth and progression using miRNA or gene therapy approaches. Combining miRNA-based therapies with conventional chemotherapy and radiotherapy may change therapeutic outcomes and overcome resistances [100]. MicroRNAs' unique expression profiles and functional roles make them valuable as diagnostic biomarkers and therapeutic targets for HNC. Further research into these miRNAs' specific mechanisms and interactions in HNC will be essential for developing effective miRNA-based therapies and improving patient outcomes (**Figure 2**).

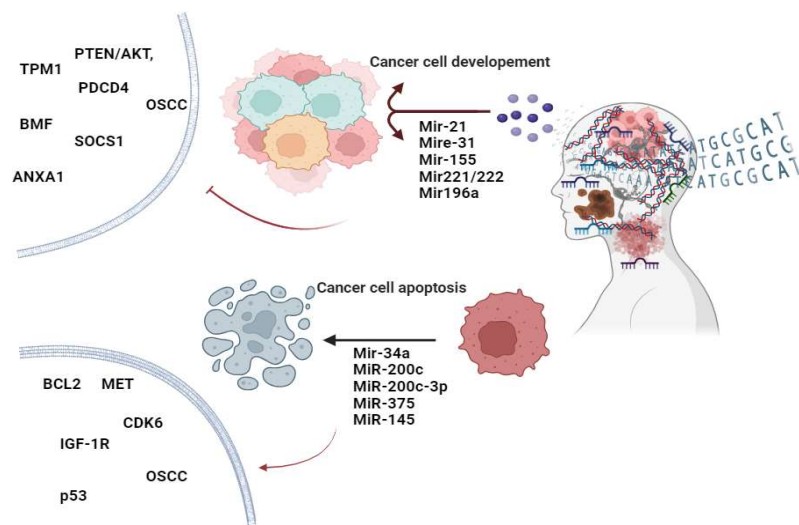


Figure 2. OncomiRs and Tumour-Suppressive miRNAs: Key Regulators in Head and Neck Cancer Progression. This figure illustrates the dual roles of oncomiRs and tumour-suppressive miRNAs in head and neck cancer. OncomiRs promote tumour growth and metastasis, while tumour-suppressive miRNAs inhibit cancer progression. Together, these miRNAs orchestrate molecular pathways in cell proliferation, apoptosis, and angiogenesis. (Created with BioRender.com).

5.3. In Silico Validation of miRNAs in Head and Neck Cancer

To validate miRNAs, the OncoMir database (<https://oncomir.org/>) was utilized. This validation revealed that among the oncomiRs, hsa-miR-21-5p, hsa-miR-31-5p, hsa-miR-221-3p, hsa-miR-222-3p, hsa-miR-196a-5p, and hsa-miR-200c-3p were linked to tumorigenesis in HNSC (Table 5). For tumour-suppressive miRNAs, hsa-miR-375 and hsa-miR-145-5p were also associated with HNSC tumorigenesis (Table 6). Notably, hsa-miR-155-3p was the only miRNA significantly related to survival outcomes in HNSC (Table 7). Additionally, a strong correlation was observed between hsa-miR-155-3p and the genes RAI14, S1PR5, OSBPL10, and METTL6 (Table 8).

Table 5. miRNAs associated with tumorigenesis of HNSC.

miRNA name	P-value T-Test	FDR T-Test	Upregulated in	Tumor Log2 Mean Expression	Normal Log2Mean Expression
hsa-miR-21-5p	8.64E-15	6.65E-13	Tumour	0	0
hsa-miR-31-5p	1.12E-07	8.23E-07	Tumour	0	0
hsa-miR-221-3p	1.14E-03	3.09E-03	Tumour	0	0
hsa-miR-222-3p	2.07E-06	1.02E-05	Tumour	0	0
hsa-miR-196a-5p	2.44E-17	8.45E-15	Tumour	0	0
hsa-miR-200c-3p	1.44E-02	3.12E-02	Tumour	0	0
hsa-miR-375	1.77E-11	3.60E-10	Normal	0	0
hsa-miR-145-5p	2.44E-04	7.54E-04	Normal	0	0

Table 6. miRNAs significantly associated with survival in HNSC.

miRNA name	Log Rank P-value	Log Rank FDR	Z-score	Upregulated in	Deceased Log2 Mean Expression	Living Log2 Mean Expression	T-Test P-value	T-Test FDR
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hsa-miR-155-3p	3.46E-02	3.77E-01	1.985	Living	0.52	0.65	3.33E-01	5.94E-01
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Table 7. hsa-miR-155-3p -Target Correlation in HNSC.

Gene	Gene Description	Correlation	Correlation P-value	Correlation FDR	miRDB Score
RAI14	Retinoic acid-induced 14	-0.106	1.73E-02	5.67E-01	82
S1PR5	Sphingosine-1-phosphate receptor 5	-0.0983	2.73E-02	5.67E-01	76
OSBPL10	Oxysterol binding protein-like 10	-0.0961	3.09E-02	5.67E-01	90
METTL6	Methyltransferase like 6	-0.0876	4.93E-02	5.79E-01	63

6. Recent Studies Profiling miRNA Expression in Head and Neck Cancer Using High-throughput Technologies

Several recent studies have applied high-throughput technologies to profile miRNA expression in HNC. These technologies are advanced and evaluate the comprehensive and large-scale analysis of miRNA molecules. Using these technologies, the roles of miRNAs have been revealed in cancer development, progression, and their potential therapeutic applications. Some of the key high-throughput technologies for miRNA profiling are Next-Generation Sequencing (NGS), RNA-Seq (Total RNA Sequencing), Microarrays, Quantitative Real-Time PCR (qRT-PCR), Digital PCR (dPCR), NanoString nCounter Analysis and Microfluidics-based Platforms. The following are selected examples of recent achievements in finding key miRNAs in HNC using the aforementioned methods. In 2017, Ganci et al., identified 35 miRNAs deregulated in both tumour and peri-tumoral tissues in head and neck squamous cell carcinoma patients using microarray hybridization, reverse transcription of miRNAs and qPCR. This identification of predictive miRNA signature would be crucial for early detection, following up, and treatment strategy for the head and neck squamous cell carcinoma patients [101]. In 2023, three-miRNA panel has identified the potential for the diagnosis of HNSCC from the patients’ plasma. As this research indicates, miR-95-3p and miR-579-5p expression upregulated, and miR-1298-3p downregulated in the plasma of HNSCC patients significantly. This investigation shows a convenient diagnostic and screening tool for head and neck cancer early detection [102]. Another method is dPCR which assists patients with cancer of unknown primary site (CUP). Laprovitera et al., predicted the primary site of 53 CUPs using a molecular assay, based on digital miRNA profiling. Furthermore, HNC with metastases of known origin was assessed in this study and the unknown sites were identified in the CUP patients using dPCR. High-throughput technologies have revolutionized miRNA profiling in HNC. These methods provide comprehensive, sensitive, and quantitative data that are essential for understanding miRNA roles in cancer and developing diagnostic and therapeutic strategies [103]. Each technology has its unique advantages, and the choice of method depends on the specific research question, available resources, and the desired resolution of the miRNA profiling. These unique methodologies have identified numerous miRNAs expressed in various HNC subtypes providing sensitive and precise miRNA profiling for improvement of HNC diagnostic and therapeutic approaches.

Despite all these advancements, HNC is still diagnosed at advanced stages in many cases, generating limited improvements in survival rates. The improvement of miRNA therapeutics in HNC faces several limitations such as: contradictions in study results, miRNAs specificity issues, limited understanding of tumour microenvironment (TME), heterogeneity in molecular subtypes of HNC, lack of effective biomarkers for early detection, resistance of miRNAs to radio and chemo-therapies, HPV-positive vs. HPV-negative HNC, detection and prognostic challenges of miRNAs and epidemiological study limitations [104]. These limitations highlight the need for further research to improve the specificity and reliability of miRNA-based diagnostics and therapeutics in HNC.

However, there are several promising fields that the future of profiling miRNA in HNC can be focused on. Investigating the miRNA profiles specific to different anatomical sites of HNC (miRNA signature) is a promising approach that can help identify unique biomarkers and therapeutic targets [105]. In addition, detecting miRNA through liquid biopsies, such as saliva or blood samples is a non-invasive diagnostic and prognostic tools for HNC, potentially allowing for early detection and monitoring of treatment response in HNC [106,107]. Optimization of delivery mechanisms and the stability of miRNA therapeutics are paramount in the progress of wide application of miRNAs in HNC [107]. Moreover, integrating miRNA profiling with comprehensive genomic and transcriptomic data will provide insights into the molecular mechanisms driving HNC. Ultimately, immunotherapy is a very promising approach for the future of HNC treatment. Studying how miRNAs interact with the immune system in HNC and identifying miRNAs that enhance immune response or serve as biomarkers for immunotherapy are fundamental in shaping the future of miRNA therapeutics research in HNC [106].

In summary, research into miRNA profiling in head and neck cancer offers exciting opportunities to improve diagnosis and treatments. By focusing on specific miRNA profiles, integrating with genomic data, and exploring non-invasive diagnostic methods, uncovering new insights and therapeutic targets will be possible. All these efforts ultimately serve enhancing patient care and outcomes.

7. Future Perspectives

Precision medicine in HNC detection and treatment focuses on tailoring treatment to individual genetic profiles. In HNC, identifying specific genetic mutations and viral associations, particularly with HPV, has led to the development of targeted therapies and vaccines designed to improve patient outcomes. For example, the presence of HPV in oropharyngeal cancer has been associated with a better prognosis and response to certain therapies. Targeted treatments, such as those directed against the epidermal growth factor receptor (EGFR), and the use of HPV vaccines are key advances in the precision medicine approach to HNC [10].

The future of precision medicine lies in further integrating genomic, transcriptomic, metabolomic, and proteomic data to enable personalized treatment approaches [108,109]. Combining these different data types allows clinicians to develop more effective, individualized treatment plans that improve patient outcomes and reduce adverse effects. In HNC, research has focused on targeting EGFR with monoclonal antibodies such as cetuximab and exploring the therapeutic potential of inhibiting the PI3K/AKT/mTOR signalling pathway. These signalling pathways are critical for regulating cell growth, survival, and proliferation, and their dysregulation is a hallmark of many cancers. In addition, immunotherapy based on checkpoint inhibitors, such as pembrolizumab and nivolumab, is increasingly recognized as a potential treatment strategy in HNC. These therapies use the patient's immune system to recognize and destroy cancer cells, offering a new avenue for treatment, especially in cases where conventional therapies have failed [14,110].

Laboratory studies and computer-based data analyses are at the forefront of revolutionizing cancer research and the treatment of HNC. Through use of artificial intelligence (AI) and machine learning (ML) analysis of large data sets can potentially discover new biomarkers, predict treatment outcomes, and personalize treatment plans. These technologies can process and interpret vast amounts of genomic and clinical data, identifying patterns and correlations that may not be apparent using traditional methods. Big data analytics enable the integration of different data types and provide comprehensive insights into cancer biology and treatment responses [111]. In addition, developing digital health tools and wearable technologies for real-time patient monitoring offers new opportunities to improve quality of life and treatment adherence. These tools can track vital signs, medication adherence, and symptom progression, enabling timely interventions and adjustments to treatment plans. Integrating these technologies into clinical practice is expected to accelerate the pace of discoveries in cancer research and change the perspective of cancer care so that treatments become more personalized and responsive to individual patient needs [112].

The future of HNC research and treatment is poised for significant advances through precision medicine, new therapeutic targets, and the integration of technology and data science. These developments promise to improve patient outcomes, personalize cancer treatment, and ultimately change the approach to treating these complex diseases. The continued evolution of precision

medicine, driven by genomic, transcriptomic, metabolomic, and proteomic insights, will likely lead to more targeted and effective treatments. The discovery and validation of novel therapeutic targets will expand the arsenal of available treatments. At the same time, advances in AI, ML, and digital health technologies will improve the precision and personalization of cancer care. Integrating these innovative approaches will be instrumental in minimizing overdiagnosis and overtreatment, improving survival rates, and enhancing quality of life for patients with HNC. Collaboration between researchers, clinicians, and technicians will be crucial in realizing the full potential of these advancements and ensuring that each patient receives the most effective and personalized therapy.

8. Conclusions

This review has revealed substantial advancements in deciphering the molecular complexities of HNC. It emphasizes the central role of biomarkers and genetic alterations in the diagnosis and prognosis of these malignancies. Advances in precision medicine, new therapeutic targets, and the integration of technology and data science will revolutionize the treatment strategies for HNC. Identifying specific biomarkers and genetic signatures has not only improved diagnostic accuracy but also facilitated the development of targeted therapeutic interventions. This gives hope for personalized treatment strategies to improve patient outcomes while minimizing toxicity.

The molecular understanding of HNC has contributed significantly to cancer therapy development. By deciphering the genetic and epigenetic changes underlying these cancers, researchers have identified key pathways and targets for intervention. These molecular insights are crucial for developing more effective, less harmful treatments and overcoming resistance to current therapies. They mark the transition from a one-size-fits-all approach to a more nuanced, patient-specific strategy in cancer treatment and emphasizes the need for comprehensive molecular diagnosis as the cornerstone of effective cancer management. Considering these advances, there is a critical need for continued research and collaboration within the oncology community. Multidisciplinary efforts that combine the expertise of molecular biologists, clinicians, data scientists, and patient advocates are essential to further unravel the complexities of HNC. Such collaborative efforts will not only accelerate the discovery of new biomarkers and therapeutic targets, but also ensure the rapid translation of these findings into clinical practice, ultimately improving patient care. These collective efforts are vital to overcoming the remaining challenges in the treatment of HNC, including drug resistance, metastasis and recurrence. The oncology community is therefore called upon to foster an environment of innovation, collaboration, and shared knowledge with the ultimate goal of defeating these formidable diseases. Although significant progress has been made in the molecular characterization and treatment of HNC, the path forward requires sustained research, innovation, and collaboration. As we continue to explore the molecular basis of these cancers, the oncology community can look forward to a future where cancer treatment is not only effective but also personalized, transforming the prognosis for patients worldwide. Advances in precision medicine, the exploration of novel therapeutic targets, the integration of cutting-edge technology, and data science will collectively drive this transformation and ensure that each patient receives the most effective and personalized care and treatment.

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