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Review

# Nutritional and Molecular Challenges in Head and Neck Cancer: A Dual Front in Therapeutic Targeting and Drug Delivery

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## Abstract

Head and neck cancer (HNC) is a heterogeneous and complicated category of malignancies with a high rate of tumor biology and a high morbidity rate related to treatment. In addition to genetic and molecular changes, patients with HNC often have severe nutritional and biochemical imbalances, such as hypoalbuminemia, anemia, and nutrition-related malnutrition related to cancer, which have a significant impact on the further course of the disease, its response to treatment, and clinical outcomes. Hypoalbuminemia changes drug pharmacokinetics and tissue distribution, anemia affects tumor oxygenation, radiotherapy efficacy and radically affects malnutrition effects on immune competence and treatment tolerance on drug delivery and precision therapy. Various signalling pathways like epidermal growth factor receptor pathway, PI3K-AKT-mTOR and mitogen-activated protein kinase pathway help in tumor survival/proliferation and therapy resistance thus are critical as a target of therapeutic action. There is also emerging evidence of the involvement of non-coding RNAs (ncRNAs) and epigenetic biomarkers in the regulation of tumor behavior and treatment sensitivity and disease prognosis which provide new opportunities in the context of personalized medicine in HNC. The development of drug delivery vehicles like monoclonal antibodies, nanoparticle-based-vehicles, and optimized oral and intravenous preparations are focused on increasing the specificity of the therapeutic action and reducing the systemic toxicity. Nonetheless, the effectiveness of such interventions strongly depends on the nutritional and biochemical condition of a patient and this is why the combination of these approaches is crucial. This review highlights the two-fold task of targeting molecular pathways but at the same time treating nutritional and biochemical deficiencies and its recommendation is a holistic, patient-centered model to enhance therapeutic targeting, drug delivery, and clinical outcomes in head and neck cancer.
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**Keywords:**
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## 1. INTRODUCTION

Head and neck cancers (HNCs) represent a heterogeneous group of cancers that develop in the tissues of the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, and salivary glands. Most of these tumors develop out of the squamous mucosal-lining epithelial cells of the upper aerodigestive tract and are thus termed head and neck squamous cell carcinomas (HNSCCs). Even though it is also possible to have cancers occurring due to the salivary glands, sinuses, muscles, or nerves of the head and neck, they are significantly fewer as compared to squamous cell carcinomas. Head and neck cancers can arise in a variety of different subsites which have different clinical behaviors and therapeutic concerns. Examples of structures that are found in the oral cavity are the lips, anterior two-thirds of the tongue, gums, buccal mucosa, hard palate, and floor of the mouth. The pharynx, a 5 inch muscular tube, which connects the nasal cavity to the esophagus is further subdivided into the nasopharynx, oropharynx, and hypopharynx. The larynx that is directly below the pharynx, has the vocal chords and is a key component in the phonation process as well as protection of the airways through the epiglottis. Other areas are the paranasal sinuses and nasal cavity and major and minor salivary glands which produce saliva.

HNC's are a major societal problem in the world. In the United States, they are associated with almost 4 percent cancer diagnoses, where men are mostly affected compared to women and most of them are older than 50 years **[1].** Over 68,000 new cases in 2021 alone were estimated, most of them in oral cavity, pharynx or the larynx. The paranasal sinuses, nasal cavity and salivary glands cancers are relatively uncommon. Malnutrition and cancer cachexia are prevalent and debilitating complications among the patients with HNC. Different studies indicate 25%-65% of patients with HNC who present with malnutrition at diagnosis, which is frequently characterized by greater than 10% decrease in body mass, is caused by tumor- and host-produced cytokines, which stimulates both systemic inflammation and energy expenditure in addition to protein and lipid metabolism alterations **[2].** Oncologic interventions, especially radiotherapy and chemotherapy, also increase weight loss, anorexia, dysphagia, mucositis, and changes in taste, which greatly aggravate the state of nutrition. The clinically significant aspects of malnutrition in the treatment of HNC are significant. Radiation-induced weight loss does not only reduce the safety and the effectiveness of cancer treatment but also with low quality of life (QoL), worsened physical functioning, greater treatment disruptions, and lower survival rates. The personal, social and healthcare costs of these are massive. Nonetheless, due to the multifactoriality of cancer cachexia and the presence of complicated biological and behavioral processes, it is still difficult to conduct high-quality clinical nutrition research in the target population of patients. Considering such, it is important to understand the interaction between head and neck cancer, treatment-related toxicities, and nutrition to enhance the clinical outcomes. This review examines the epidemiology, pathology, and clinical effects, as well as the management of malnutrition in head and neck cancer patients, and describes the present gaps and future perspectives of the supportive care.

## 2. NUTRITIONAL AND BIOCHEMICAL CHALLENGES IN HNC

HNC patients have severe nutritional and biochemical imbalances caused by tumor biology, local anatomical and treatment toxicities. The inflammation caused by tumors, metabolic stress, and catabolism mediated by cytokines overlaps with dysphagia, mucositis, xerostomia, and pain and grossly impairs the nutritional status. These changes are common and occur as hypoalbuminemia, anemia, and progressive malnutrition, all of which are closely related to treatment breaks, reduced tolerance to chemoradiation, wound healing, and survival.

### 2.1 Hypoalbuminemia

Systemic inflammation, poor protein intake, and high metabolic turnover are common in HNC patients, which lead to hypoalbuminemia. Pro-inflammatory cytokines (IL-6, TNF-a) inhibit albumin production by the liver and, at the same time, raise the capillary permeability and catabolism. Low serum albumin is associated with more postoperative problems, deficiency in radiotherapy tolerance, low immunity, more infections, and worse overall survival. Hypoalbuminemia is a common occurrence with HNC, which is an expression of systemic inflammation and poor nutritional condition. The hepatic albumin synthesis may be inhibited by inflammatory cytokines (e.g., IL-6, TNF-a) and augmented capillary permeability and catabolic turnover, and suboptimal protein intake may also contribute to further worsening of hypoalbuminemia. Reduced pretreatment serum albumin - usually taken to be less than 3.5 g/dl has been demonstrated repeatedly to be associated with poor clinical outcomes. Pretreatment albumin of less than 3.5 g/dl was also independently linked to a significantly lower disease-free, cancer-specific and overall survival in a prospective cohort of treatment-naive patients with HNSCC **[3].** Similarly, in a large retrospective surgical series of 604 HNC patients, lower preoperative albumin was linked to a higher rate of

postoperative wound infections and poorer overall survival **[4].** The preoperative albumin level is also a prognostic factor as in one retrospective study of HNSCC patients, a preoperative serum albumin level that is less than 2.8 g/dl on the first postoperative day was a significant predictor of increased risk of postoperative major wound infection, free-flap failure, and overall, disease-specific, and disease-free survival **[5, 6].** Combined, this results in an indication that serum albumin is a strong prognostic biomarker in HNC and is not simply a reflection of nutritional deterioration but also a manifestation of the system disease burden and inflammatory condition, and an indicator of greater risk of complications, decreased treatment tolerance, and poorer prognosis.

### 2.2 Anemia

Anemia is a common and clinically relevant complication of HNC that occurs due to a multiplicity of interacting factors such as long-term inflammation, micronutrient deficiency (iron, folate, vitamin B12), tumor blood loss, and bone-marrow suppression caused by chemoradiation. The result of the stimulated production of hepcidin and effects of inflammatory cytokines, like IL-6, to interfere with iron release by macrophages and intestinal absorption, eventually causes functional iron deficiency and impairment of erythropoiesis, a well-established mechanism in the anemia of chronic disease. It is established that anemia at baseline or acquired during treatment has negative impact on the outcomes of the treatment. In a big prospective trial of patients with HNSCC, low pretreatment hemoglobin was statistically linked with worse locoregional control as well as worse overall survival and, in a trial assessing radiotherapy responses, hemoglobin levels less than 12 g/dL was statistically linked with reduced oxygenation of the tumor, thus, striking worse tumor control rates **[7, 8].** The chemoradiation also worsens anemia by reducing erythropoiesis as is seen in a group of HNC patients undergoing concurrent treatment with treatment-induced anemia being associated with more fatigue, worse quality of life, and lower rates of therapy adherence **[9].** Altogether, these results demonstrate that anemia is a valuable disease burden biomarker, systemic inflammation, and treatment tolerance predictor in HNC. This not only aggravates fatigue and functional status in the presence of radiotherapy but also interferes with the effectiveness of radiotherapy, because of the lack of tumor oxygenation, which eventually leads to worse oncologic outcomes.

### 2.3 Malnutrition

Malnutrition and nutritional deficits among such patients are one of the major causes of the high burden of the HNC disease, which impact not only the results of health but also the overall quality of life **[10].** Nutrition issues already initiate disease and different researchers have reported that 25%-65% the HNC patients present themselves with malnutrition syndrome with over 10% weight loss due to normal body mass **[11].** A large group of HNC patients studied by Kubrak et al. showed that tumor stage; classes of dietary intake, and performance status were independent predictors of weight loss in an ignorant population **[12].** According to various studies, tumor stage, classes of dietary intake, and performance status have demonstrated to be the independent predictors of malnutrition in HNC patients during treatment with high percentage rates of up to 80% **[13].** In context to therapeutic interventions, it has been observed that two adverse effects of radiotherapy that are extremely frequent and may occur alongside thick saliva are xerostomia and the impaired functioning of the parathyroid gland that considerably diminish the quality of life of the patient. This has additional adverse effects on the chewing, swallowing, and speaking functions, and a corresponding rise in infections **[14].** Nausea, vomiting, constipation, depression, dysgeusia, and odynophagia are also among the other side effects of the therapeutic modalities that seriously affect weight maintenance and proper healing process **[15].** Proper nutrition of patients with HNC is critical, as malnutrition is linked to a reduction in therapeutic and immunological response with an increased rate of infections and post-operative complications. By virtue of poor nutrition uptake, such patients will suffer weight loss, muscle mass loss, fatigue, and anemia that culminates in the cancer cachexia syndrome. Research has shown that a poor nutrition status is observed in 25%-27% of these patients at the diagnosis date and before the initiation of treatment **[16].** It was also demonstrated that pretreatment weight loss is a powerful survival indicator, and pretreatment cachexia is related to unfavorable survival. Also, sarcopenia resulting due to cancer cachexia has been linked to poor treatment outcomes among head and neck cancer patients **[17].** The process of cancer treatment may also lead to the worsening of treatment-related dysphagia, which leads to decreased food intake and worsened nutrition status.

## 3. MOLECULAR TARGETS AND THERAPEUTIC INNOVATIONS IN HNC

### 3.1 Epidermal growth factor receptor (EGFR) Pathway

Genome sequencing analysis has shown significant changes in the multi-step process of HNC formation involving the accumulation of mutations in the primary cellular signaling pathways that control angiogenesis, proliferation of cells,

survival, and immune system functions [18]. EGFR belongs to the ErbB/HER receptor family and acts as a receptor tyrosine kinase (RTK) [19]. The EGF (ligand) binds with the receptor to form EGFR and combines with other members of the Erb family (ErbB2, ErbB3, and ErbB4) to form a homodimer or heterodimer, which triggers downstream signaling via the PI3K/AKT/mTOR pathway and the mitogen-activated protein kinases (MAPKs) cascade. This causes specific genes in the cell nucleus to become active; activated transcription factors lead to promoting angiogenesis and metastasis. EGFR overexpression is found in around 90% of HNSCC cases; since it makes the tumor bigger, less sensitive to radiation, and more likely to recur, it is regarded as a bad prognostic factor [20].

According to a number of studies examining the relationship between EGFR overexpression and survival, lower HNSCC survival is linked to higher tumor EGFR protein expression as determined by immunohistochemistry (IHC). EGFR activation along with tyrosine kinases mediates the phosphorylation cascade. This cascade stimulates angiogenesis, invasion, proliferation, and metastatic dissemination by acting downstream through the PI3K–PTEN–AKT, MAPK, ERK, and Jak/STAT pathways. Several processes, such as overexpression of EGFR and its ligands, the formation of autocrine/paracrine loops, EGFR gene amplification, EGFR mutation/polymorphism, and transactivation by other RTKs, can cause aberrant activation of EGFR signaling in HNSCC [21]. The development of cetuximab in both curative and palliative settings and the execution of multiple trials with other antibodies targeting EGFR, involving downstream EGFR signaling, were made possible by the significance of the EGFR pathway in HNSCC [22-24].

Recent translational and clinical research has focused on combining EGFR inhibitors with chemotherapy, radiation, and immune checkpoint inhibitors in order to overcome resistance and enhance patient outcome. In addition, accumulating evidence suggests that combining EGFR inhibitors with immune checkpoint inhibitors, particularly PD-1/PD-L1 blockers, can boost anticancer immune responses by altering the tumor microenvironment and boosting immune cell penetration. These combination techniques are a promising approach to overcoming acquired resistance to EGFR-targeted therapy and achieving more long-term clinical outcomes in patients with advanced HNSCC [25]. A systematic study indicated that exon 19 deletions and the L858R substitution constitute around 25% (22% and 2.5%, respectively) of all EGFR mutations in HNSCC, compared to approximately 50% in Non-Small Cell Lung Cancer (NSCLC) [26]. Cetuximab, an anti-EGFR monoclonal antibody, was used in conjunction with pembrolizumab in patients with HNSCC. The Phase II study has also shown an impressive ORR of 45%, emphasizing the significance of EGFR inhibition paired with anti-PD-1 therapy in HNSCC [27]. In patients receiving pembrolizumab for recurrent or metastatic HNC, afatinib (an irreversible EGFR tyrosine kinase inhibitor) has been shown to improve outcomes by stimulating immune activation and antigen presentation in the tumor microenvironment [28]. The EGFR pathway is a major oncogenic driver that encourages invasion, proliferation, survival, and resistance to HNC treatment. Despite the prevalence of EGFR overexpression, therapy outcomes are still inconsistent. New approaches that combine immunotherapy, radiation, and chemotherapy offer intriguing ways to enhance clinical results **(Figure 1).**

### 3.2 PI3K–AKT–mTOR Pathway

Lipid kinases called phosphoinositide 3-kinases (PI3Ks) change PIP2 into PIP3, which triggers (PI3K)/Protein Kinase B (AKT) and subsequent survival pathways. Class I PI3Ks, particularly the p110α isoform encoded by PIK3CA, are important therapeutic targets because they are often altered in malignancies, including HNC, enhancing proliferation, metabolism, and therapeutic resistance. PI3K-generated PIP3 activates AKT, a serine/threonine kinase that controls angiogenesis, growth, metabolism, and cell survival [29]. AKT is a crucial therapeutic target in HNC because it is often hyperactivated due to PIK3CA mutations, PTEN loss, or RTK signaling, which promotes tumor development, Epithelial-Mesenchymal Transition (EMT), and resistance to chemotherapy and radiation. Mechanistic Target of Rapamycin (mTOR), a key serine/threonine kinase, controls cellular growth, protein synthesis, metabolism, and survival via the mTORC1 and mTORC2 complexes. In HNC, mTOR is often hyperactivated through PI3K/AKT signaling, which fosters tumor progression, angiogenesis, and treatment resistance; this makes it a crucial target for therapeutic inhibitors like everolimus and temsirolimus. By phosphorylating several target proteins involved in survival, metabolism, and cell-cycle regulation, AKT controls several cellular processes. Important targets of AKT include GSK-3α/β (cell-cycle progression), BAD, BIM, and caspase-9 (anti-apoptotic regulation), mTORC1 regulators TSC1/2, FOXO transcription factors (cell survival and stress response), MDM2 (p53 suppression), and AS160 (glucose uptake). Through these targets, AKT stimulates angiogenesis, metabolic reprogramming, proliferation, and resistance to treatment in HNC [30].

Phosphatase and tensin homolog, or PTEN, is a tumor suppressor that inhibits AKT activation by dephosphorylating PIP3 to PIP2, hence adversely regulating the PI3K/AKT/mTOR pathway.

One of the most commonly dysregulated pathways in HNC is the PI3K/AKT/mTOR signaling axis, which is linked to angiogenesis, tumor development, survival, metabolism, and resistance to treatment. Upstream RTKs, such as EGFR, HER2/HER3, IGF-1R, and FGFR, are often overexpressed or hyperactivated, which triggers the PI3K/AKT/mTOR pathway. Class I PI3Ks, which are made up of a catalytic p110 subunit (often p110α encoded by PIK3CA) and a regulatory p85 subunit, are recruited by adaptor proteins such as IRS1/2 and GRB2 upon ligand binding and receptor autophosphorylation. By catalyzing the transformation of PIP2 into PIP3, activated PI3K creates a membrane docking site for AKT. Following phosphorylation by PDK1 (Thr308) and mTORC2 (Ser473), AKT is fully activated [31]. Numerous substrates that regulate protein synthesis, cell-cycle development, glucose metabolism, and cell survival are phosphorylated by activated AKT. While mTORC2 controls cytoskeletal architecture and strengthens AKT signaling, one of the important downstream nodes, mTORC1, stimulates cellular growth and proliferation by phosphorylating S6K1 and 4EBP1, improving mRNA translation and ribosome synthesis. By dephosphorylating PIP3 back to PIP2, the tumor suppressor PTEN acts as a crucial negative regulator; nevertheless, PTEN loss or downregulation—common in HNC—maintains AKT activation. In HNC, sustained activation of this system is driven by mutations in PIK3CA, PTEN suppression, and RTK overactivity. These factors contribute to oncogenesis, metabolic reprogramming, and treatment resistance.

The HNC showed that missense mutations in PIK3CA accounted for 80% of the changes [32]. Overexpression of the messenger RNA (mRNA), PIK3CA is frequently seen in HNSCC. Several PI3K regulatory subunits and other PI3K isoforms (PIK3CB, PIK3CD, and PIK3CG) also exhibit mutations and copy number gains (0.5–11%) [33]. The activation of matrix metalloproteinases (MMPs), which are a type of proteolytic enzyme involved in the degradation of the extracellular matrix, promotes cell invasion and metastasis. Out of the 23 different types of MMPs, MMP-2 and MMP-9 are two that are known to be crucial for cell invasion. The PI3K/AKT/mTOR pathway can degrade the extracellular matrix, elevate MMP-2 expression at both mRNA and protein levels, and enhances cancer cell invasion and metastasis [34]. AKT mutations were found with an overall pooled prevalence of 2% in HNC. The most common mutation was identified in the hotspot p.(E17K), resulting from a single nucleotide alteration (c.49 G > A) that replaces an E with a K at position. The meta-analysis published in 2021 indicated that the overall pooled prevalence of mTOR mutations in head and neck cancer was 3%. MTOR mutations were most frequently observed in Asia (4.1%), followed by Europe (2.3%) and North America (1.7%). Although missense mutations occurred more often, no mutation was reported more than once. Missense mutations account for forty percent of PTEN mutations, while nonsense mutations comprise 11%. The most common mutations in HNC were p.(Q171X) and the single nucleotide change c.511C > T [35].

Recent studies of molecular changes have shown that targeted molecular therapies aimed at decreasing mTOR pathway activity could produce anticancer effects in HNC [36]. Many pan-PI3Ks have been investigated in clinical settings. Buparlisib (BKM120) is a pan-PI3K inhibitor that can be used orally. BKM120 reduced PI3K activity in vivo in cell lines with wild-type PIK3CA and mutant versions containing any hotspot mutation of E542K, E545K, or H1047R. In patients with HNC, the combination of cetuximab and copanlisib, another pan-PI3Ki, showed poor toxicity and limited effectiveness [37]. The three AKT inhibitors used in HNC research are MK-2206, GDC0068, and D-21266. Ipatasertib (GDC0068) is an ATP-competitive, highly selective AKT inhibitor that is taken orally. It increases AKT phosphorylation and inhibits downstream signaling. Ipatasertib is now being tested in phase I or II trials for the treatment of HNC either alone or in conjunction with chemotherapy [38]. MEK inhibitor PD-0325901 overcomes resistance to the PI3K/mTOR inhibitor gedatolisib and potentiates anticancer efficacy in HNC cell lines [39]. The PI3K/AKT/mTOR (PAM) signalling pathway is a highly conserved transduction network found in eukaryotic cells that promotes cell survival, proliferation, and cycle advancement. Dysfunction in components of this pathway, such as PI3K hyperactivity, loss of PTEN function, and AKT gain-of-function mutations, are well-known causes of cancer treatment resistance and disease progression.

### 3.3 Mitogen-activated protein kinase (MAPK) pathway

MAPK pathway holds significant importance as a clinically significant signaling axis in HNSCC, and is emerging as an axis not easily categorized as purely an oncogenic driver. It, includes critical kinases from RAS → RAF → MEK → ERK as fundamental controllers of cell multiplication, growth and survival and is often deregulated in cancers such as HNSCC. Large-scale genomic profiling studies, and

especially analyses of The Cancer Genome Atlas (TCGA) dataset, have shown that about 18-22% of tumors in HNSCC have somatic mutations in MAPK pathway genes including HRAS, MAPK1 (ERK2), BRAF, MAP2K1/ Surprisingly, patients who have MAPK-mutant HNSCC have significantly better overall survival when compared to those with MAPK-wildtype HNSCC. Exceptionally long survival was linked to MAPK pathway aberrations in a large-scale integrative study, with the benefit itself more pronounced in tumors with concomitant TP53 mutations, a genomic change that is generally regarded as predictive of aggressive disease and poor prognosis in HNSCC. In regard to this category, the average survival was estimated to be approx. 14 years as compared to TP53-mutant/MAPK-wildtype tumors suggesting a potential role of MAPK variations as a prognostic biomarker [40]. Mechanistically, MAPK-mutant HNSCCs exhibit distinct signaling and immune properties. It is demonstrated that various types of MAPK mutations cause the inhibition of ErbB3 (HER3) phosphorylation and phosphorylation signaling, which has been reported to promote tumor growth, survival, and resistance to EGFR-targeted therapy in HNSCC. Loss of ErbB3-mediated downstream PI3K-AKT signaling probably plays a role in decreased tumor aggressiveness [40]. Simultaneously, transcriptomic and immune-profiling data indicate that MAPK-mutant tumors have a distinctively immune-inflamed tumor microenvironment, with much higher infiltration of the CD8+ cytotoxic T lymphocytes, significantly increased interferon-gamma responding gene signatures, and an increased expression of cytolytic markers, including granzyme B and perforin. Interestingly, MAPK pathway aberrations selectively when it comes to eliciting antitumor immunity, as the immune-active phenotype is not observed in tumors where the PI3K, NOTCH, or JAK/STAT pathways have been altered, highlighting the specificity of the MAPK pathway aberrations in forecasting antitumor immunity [40]. These clinical implications hold immense biological significance in targeted therapies. The substantially better outcomes reported with PD-1/PD-L1 immune checkpoint blockade when compared to MAPK-wildtype tumors have been reported in association with MAPK-mutant HNSCCs, independent of tumor mutational burden. It implies that MAPK pathway mutations can be used as predictive immunotherapy biomarkers, which is urgently needed in the HNSCC where only a subset of patients have been able to respond to immunotherapy in the long term [40]. Furthermore, there is select evidence of MAPK alterations, as MAPK1 p.D321N, as observed to be exceptional sensitivity to EGFR inhibitors like erlotinib, suggesting again the role played by MAPK status in precision therapeutic stratification [41]. Taken together, existing evidence indicates that mutations of the MAPK pathways constitute a unique molecular and immunological subclass of HNSCC, which is defined by silenced oncogenic receptor signaling, increased immune response and surprisingly long-term survival, despite the high-risk presence of TP53 mutations.

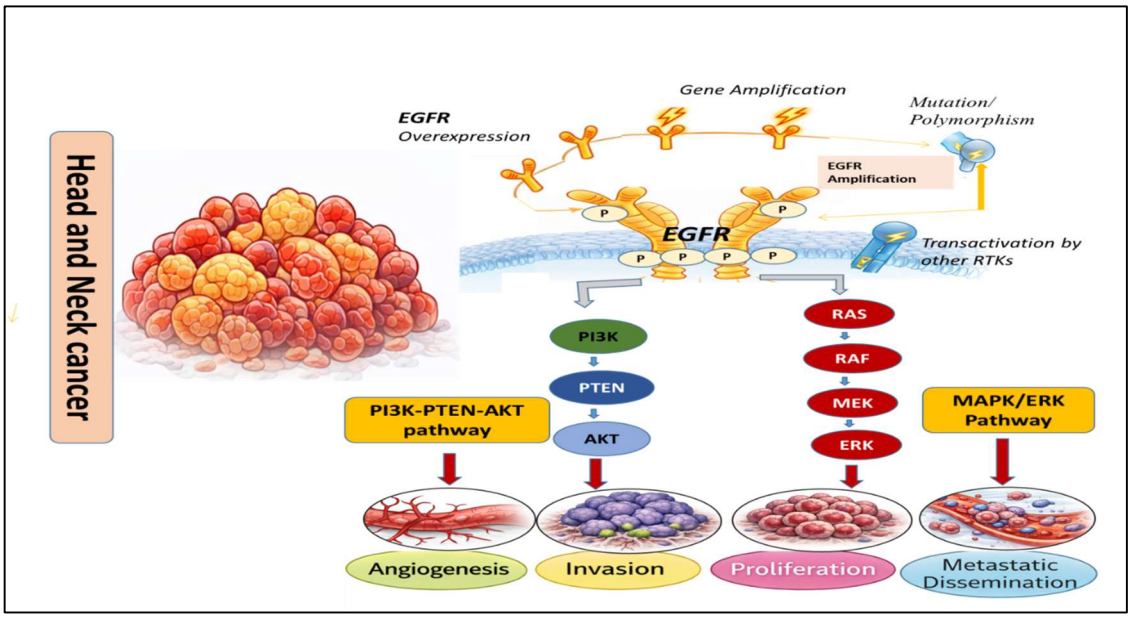


**Figure 1.** Diagrammatic representation of aberrant EGFR signaling in head and neck cancer, emphasizing EGFR dysregulation and activation of the MAPK/ERK and PI3K–AKT pathways that promote angiogenesis, invasion, proliferation, and metastasis.

### 3.4 ncRNAs and Epigenetic Biomarkers

ncRNAs, specifically, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have become essential epigenetic controllers of cancer biology, such as HNSCC. The ncRNAs control gene expression by post-transcriptional repression, chromatin remodelling, and epigenetic activity, which affects tumor initiation, progression, and response to therapy. Aberrant patterns of ncRNA expression are very cancer specific and have consistently been linked to prognosis, response to treatment and survival in HNSCC, placing them as ideal epigenetic biomarkers in precision oncology [42, 43]. miRNAs have been shown to regulate drug response in head and neck cancers by acting on apoptotic, DNA damage repair, EMT, and drug efflux pathways. The dysregulated miRNAs including miR-21, miR-155, and miR-200 and family have been indicated to play a role in resistance to the most commonly used chemotherapeutic agents like cisplatin and 5-fluorouracil through silencing tumor suppressor genes and activating survival signals including PI3K/AKT and MAPK. On the other hand, tumor-suppressive miRNAs have the capacity to reinstate chemoresistance on re-expression, which supports the importance of miRNAs as predictive biomarkers of treatment response in HNSCC [44, 45]. lncRNAs further increase the regulation complexity of epigenetic control in head and neck cancer. HOTAIR, MALAT1, and NEAT1 are oncogenic lncRNAs commonly overexpressed in HNSCC, are considered to contribute to chemotherapy resistance, radioresistance and poor clinical outcomes. These lncRNAs are able to regulate drug response via their interactions with chromatin-modifying complexes, through sponge tumor-suppressive miRNAs as competitors endogenous RNAs (ceRNAs), and by the regulation of transcription in genes related to EMT, apoptosis, and stemness. LncRNAs are appealing biomarkers predicting therapeutic efficacy and disease progression [42, 46]. The epigenetic interaction of the ncRNAs and the chromatin-modifying enzymes enhances their biomarker potential. miRNAs are able to target directly the DNA methyltransferases and histone deacetylases, thus remodeling the epigenetic landscape and shaping the response to meditation of drug. Equally, lncRNAs have the ability to attract epigenetic modifiers to certain loci in the genome which leads to the transcriptional activation or repression of genes associated with therapy. This active ncRNA-epigenetic network is the one that is decisive in the sensitivity or resistance of chemotherapy, radiotherapy, and developing targeted therapies in head and neck cancer [47]. In addition to its diagnostic and prognostic nature, miRNAs and lncRNAs are highly capable of therapy as theranostic agents, combining both diagnosis and targeted therapy. The ncRNAs in the blood, saliva, and tumor-derived exosomes are detected as minimally invasive biomarkers in the early detection, monitoring of treatment, and predicting the therapeutic response in HNSCC. At the same time, miRNA mimics, antagomiRs, and lncRNA-targeting antisense oligonucleotides have become part of the Group of ncRNA-based therapeutic strategies being investigated to reverse drug resistance and enhance treatment efficacy [46]. The development of targeted delivery systems of nanoparticles, lipid carriers, and engineered exosomes, has further accelerated this process. These delivery systems allow tumor-specific delivery of ncRNA therapeutics with reduced systemic toxicity. Combining ncRNA diagnostics with therapeutic delivery has high potential of personalized treatment in head and neck cancer, the main focus of which is overcoming resistance and enhancing patient outcomes [43, 44].

## 4. DRUG DELIVERY SYSTEMS FOR HNC

### 4.1 Monoclonal Antibodies (mAbs)

The immune system has a major impact on HNC in relation to development, invasion, progression, and metastasis. The development of immunotherapy throughout the past ten years has fundamentally changed how cancer is treated. HNC is a cancer that suppresses the immune system. It is caused by the growing tumor's impact on the tumor microenvironment; these tumor cells control the immune system, which encourages the synthesis of immunosuppressive mediators. mAbs have emerged as a promising therapeutic approach due to its less systemic side effects in target treatment. MAbs have become a commonly used immunotherapy in HNC [48]. Tumor antigen (TA), cytokines, immunological checkpoints, and tumor necrosis factor receptors are among the target-specific mAbs. The TA-targeted mAbs, such as cetuximab (an anti-EGFR mAb), have been approved and are primarily used for the treatment of HNSCC [49].

#### *4.1.1 Mechanism of mAB mediated drug delivery*

mAbs work by stimulating the immune system, especially T cells and natural killer cells. Depending on the antibody's design and target, monoclonal antibodies (mAbs) can directly attack or destroy cell membranes, impede signaling pathways, or increase immune responses. After the mAbs attach to the tumor cells, natural killer cells identify the antibody-coated tumor cells and release cytotoxic chemicals to destroy the cells. Tumor cell death is further aided by the complement system's activation upon mAb attachment to tumor cells. Additionally, mAbs can modify the immunological milieu and increase T-

cell activity to support the anti-tumor response. Additionally, mAbs can be designed to specifically target cancer cells using chemotherapy or radiation [50, 51]. MAb-mediated medication delivery for HNC targets tumor-specific or overexpressed surface antigens such EGFR, HER2, PD-L1, and CD44, allowing for highly selective therapeutic agent administration. After administration the associated medication, nanoparticle, radioisotope, or toxin accumulates preferentially at the tumor site because the mAb identifies and binds to these antigens on HNC cells with high affinity. This interaction in antibody-drug conjugates (ADCs) causes receptor-mediated endocytosis, which permits the mAb-drug complex to enter the cancer cell. Cleavable linkers within lysosomes maximize tumor destruction while reducing systemic toxicity by releasing strong cytotoxic chemicals directly into the cancerous cell [52]. Furthermore, some mAbs, like cetuximab, increase treatment efficacy by blocking signaling pathways and triggering immunological processes like antibody-dependent cellular cytotoxicity in addition to delivering medications. MAb-mediated administration is a potent tactic for enhancing treatment outcomes in HNC because it combines targeting, internalization, and targeted drug release.

#### *4.1.2 Key mAbs targeted for HNC drug delivery*

A number of important mAbs have been thoroughly investigated as targeted delivery agents in HNC due to their capacity to identify overexpressed tumor antigens. The most popular of these is cetuximab, which targets the epidermal growth factor receptor (EGFR), which is overexpressed in most HNC malignancies, making it a perfect carrier for radioimmunotherapy, drug-conjugates, and nanoparticles. Additional EGFR directed antibodies are nimotuzumab and panitumumab are crucial platforms for delivering cytotoxic drugs with less immunogenicity and enhanced specificity [53]. Trastuzumab is used in HER2-guided nanocarriers and ADCs to target HER2-positive subgroups of HNC [54]. In order to improve immune activation and target therapeutic cargo to immune-active tumor areas, immunotherapeutic antibodies such as pembrolizumab, nivolumab, and durvalumab (which target PD-1/PD-L1) are also being incorporated into hybrid delivery systems [55]. These antibodies work together to form the basis of tailored delivery techniques that are intended to increase therapeutic outcomes, decrease toxicity, and improve precision in HNC.

#### *4.1.3 mAbs based delivery platforms for HNC*

Antibody-drug conjugates (ADCs) are a popular strategy that targets antigens such as SLC3A2 (via a novel 19G4-MMAE ADC) to achieve lysosomal delivery and induce apoptosis in preclinical models. ADCs are chemically linked to mAbs to deliver potent cytotoxic drugs to cancer cells. [56] mAbs are used in another clinically investigated ADC modality to target common HNC antigens; current studies emphasize the potential and difficulties of ADCs in HNSCC, including problems such payload toxicity and antigen heterogeneity[57]. Furthermore, technologies that functionalize mAbs onto nanoparticles through nanoengineering are being developed: In HNC cell lines, cetuximab (anti-EGFR)-conjugated polymeric nanoparticles delivering the PI3K inhibitor alpelisib demonstrated efficient tumor targeting [58]. Together, these platforms show the potential of mAb-based delivery in HNC by addressing the shortcomings of existing treatments by combining specificity, targeted internalization, and modular payload design.

### 4.2 Nanoparticles

Nanoparticle-based drug delivery methods have drawn a lot of attention in the field of HNC due to its potential to elevate the activity of tumor site drug targeting, reduce systemic toxicity, and permit regulated or stimuli-responsive drug release. These nanosystems can be planned for either active targeting with ligands specific to tumors or passive targeting via the increased permeability and retention effect [59].

#### *4.2.1 Lipid nanoparticles*

Lipid nanoparticles mainly liposomes, nanostructured lipid carriers and solid lipid nanoparticles are biocompatible and can encapsulate both hydrophilic (loving water) and hydrophobic (loving fat) medicines, are commonly used to improve drug delivery. The most widely used drug carriers and the most prominent FDA-licensed nanoparticle drug delivery technique for clinical usage in nanoparticle-mediated drug delivery are liposomes [60]. Liposomal cisplatin, doxorubicin, and paclitaxel (Liposomal formulated drugs) increases drug circulation time and also enhance its solubility and stability. Liposomal drug delivery improves tumor penetration and lowers mucosal toxicity in HNC, which makes it useful for chemoradiotherapy combinations [61].

#### *4.2.2 Polymeric nanoparticles*

The basic components of polymeric nanoparticles are an aqueous medium, surfactants, and polymers, they are macromolecules made up of repeating monomeric units. Polymeric nanoparticles are mainly PLGA, PEGylated nanoparticles, dendrimers, and polymeric micelles, provide sustained and regulated drug release. These nanoparticles

aggregate at the tumor site either through active targeting methods that use ligands that bind to overexpressed receptors on HNC cells (EGFR, CD44) or passive targeting via the increased permeability and retention effect [62]. They can also alter carcinogenic pathways (such as EGFR and PI3K/Akt) by co-delivering chemotherapeutics with siRNA or miRNA. In preclinical studies, PLGA nanoparticles containing curcumin or cisplatin have demonstrated enhanced tumor accumulation and decreased nephrotoxicity in HNC [63]. A new 5-fluorouracil (5-FU) carrier in HNSCC preclinical models made of polycaprolactone microparticles and chitosan solution was studied. The findings indicate that CS-decorated PCL MPs may be useful as a 5-FU-delivery carrier to enhance the therapeutic management of HNSCC [64]. The therapeutic efficacy of intratumorally administered tailored nanoparticles incorporated into a chitosan/β-glycerophosphate hydrogel, which significantly inhibited HNC formation, was shown by in vivo studies in a xenograft mouse model [63]. Using a unique polyelectrolytic complexation technique, researchers created and refined a chitosan-alginate nanoparticle system that encapsulates simvastatin and their results indicated that simvastatin's therapeutic potential was enhanced by the chitosan-alginate nanoparticle system in tongue carcinoma [65]. According to the study, PTX-loaded nanoparticles greatly improved antitumor efficacy, as shown by decreased tumor volume, increased apoptosis, and increased oxidative and nitrosative stress in tumor tissues [66]. The advancement of clinical translation will depend on ongoing research into stimuli-responsive polymers, active targeting ligands, and multifunctional platforms. Polymeric nanoparticles are positioned to play a revolutionary role in the accurate and efficient management of HNCs with continued innovation and clinical validation, providing fresh hope for enhanced patient survival and quality of life.

#### *4.2.3 Gold Nanoparticles (AuNPs)*

Gold nanoparticles are powerful agents for photothermal treatment and radiosensitization because of their special optical and physical characteristics. Because of their high atomic number, radiation dose deposition is improved, increasing the effectiveness of radiotherapy in HNC. Moreover, determining the precise boundary between the tumor and the healthy tissue is one of the most difficult tasks for surgeons. As a result, functionalized AuNPs have been designed to target tumor tissues, delineate the boundaries of remaining normal tissues, offer targeted molecular imaging, facilitate intraoperative detection of surgical resection margins, and track the prognosis of oral cancer following treatment. AuNPs coated with cysteamine and folic acids were employed for molecular computed tomography imaging in a xenograft nude mouse nasopharyngeal HNC model. The results showed that this molecular CT imaging technique was sensitive enough to identify even tiny tumor sizes using increased X-ray signals, and the authors recommended using this method for micrometastasis screening [67]. Using AuNPs and EGFR antibodies, Liu et al. created a terahertz metamaterial biosensor that showed a greater frequency shift range and higher sensitivity detection for EGFR overexpression even at low sample concentrations [68]. Piccolo et al. created a diamond target beam (DTB) system to increase the amount of low-energy photons to produce AuNPs in vivo using a zebrafish xenotransplantation model and in vitro utilizing head and neck tumor cell lines. The researchers found increased tumor cell death in zebrafish xenografts and reduced HNC cellular viability in vitro [69].

#### *4.2.4 Magnetic Nanoparticles*

Iron oxide nanoparticles in particular facilitate magnetically directed medication delivery and magnetic hyperthermia, a condition in which localized heat causes tumor cell death. Study performed by applying an alternating magnetic field can produce hyperthermia through magnetic heating of iron oxide nanoparticles. In vivo studies employing mice xenograft models demonstrated that the tumor center's temperature was rapidly raised, resulting in hyperthermia-mediated cell death by oncotic necrosis [70]. Fmp-IO-Pc 4 NP clearly outperforms both the nontargeted Fmp-IO-Pc 4 NP and the free medication Pc 4 in terms of therapeutic efficacy and biodistribution, concluded that it has a tremendous potential to treat head and neck cancer by improving MRI contrast and photodynamic therapy performance while lowering nonspecific toxicity [71]. When paired with external magnetic fields, magnetic nanoparticles have been investigated for targeted administration of siRNA and chemotherapeutics in HNC, increasing tumor regression [72]. Theranostic nanoparticles use materials such as quantum dots, iron oxide, or gold-based nanoprobes to combine therapy with imaging (MRI, CT, PET, and fluorescence). Personalized therapy for HNC is made possible by these technologies, which enable real-time observation of tumor targeting, medication distribution, and treatment response. Iron-oxide (magnetic) nanoparticles designed for theranostics allow for magnetic hyperthermia or magnetically guided drug delivery in addition to MRI tracking; recent research has optimized their photoconversion/heat-generation and investigated combinations with chemotherapy or photodynamic agents for deeper HNC lesions.

- ***Benefits of drug delivery system in HNC***

Drug-delivery systems (DDS) provide major therapeutic benefits for HNC by increasing the accuracy, safety, and effectiveness of anticancer treatments. Nanoparticle-based vehicles like liposomes, polymeric systems, and monoclonal antibody-mediated delivery facilitate improved tumor targeting, leading to increased intratumoral drug accumulation and decreased systemic toxicity **[73].** This process takes place through active and passive (enhanced permeability and retention, EPR) ligand mediated pathways. Additionally, DDS enhances the pharmacokinetics and bioavailability of chemotherapeutics that would otherwise be quickly broken down or poorly absorbed, enabling regulated or sustained release for extended therapeutic effect [74]. These methods improve treatment acceptability and patient quality of life by reducing side effects such mucositis, nephrotoxicity, and hematologic toxicity—common drawbacks of traditional chemotherapy. Clinical decision-making is further improved by advanced platforms like theranostic nanoparticles, which provide real-time imaging, treatment monitoring, and tailored therapy [75]. Overall, DDS is essential for improving survival rates in HNC, enabling combination therapy, and overcoming drug resistance.

- ***Drawback of drug delivery system in HNC***

DDS in HNC have therapeutic potential, but there are a number of obstacles that limit their clinical application and efficacy. The thick extracellular matrix of HNC tumors is poorly penetrated by several nanocarriers, including liposomes, polymeric nanoparticles, and metallic formulations [76]. This leads to uneven drug distribution and a less than ideal treatment response. Bioavailability is further decreased by biological obstacles such as opsonization, fast clearance by the reticuloendothelial system, and buildup of off-target material in the spleen and liver. Certain DDS, particularly those made of non-biodegradable materials, may cause long-term toxicity, persistent inflammation, or immunogenicity. Routine clinical application is further hampered by manufacturing and regulatory issues, such as high production costs, complicated fabrication procedures, restricted scalability, and batch-to-batch variability [77]. Furthermore, human HNC exhibits extremely contradictory results when compared to preclinical models due to the increased permeability and retention effect, which is a key explanation for nanoparticle accumulation in tumors. Extensive use of DDS-based treatments in HNC is further delayed by a lack of clinical trial data, questionable cost-effectiveness, and the challenge of selecting individuals who might benefit most [78].

### 4.3 Oral vs IV Therapies

#### *4.3.1 Oral Administration of Therapeutic Agents in HNC*

Oral medication delivery is becoming an increasingly essential therapeutic approach in HNC, particularly with the introduction of targeted treatments and metronomic regimens that enable for long-term outpatient care. Oral administration, as opposed to intravenous treatment, is more convenient, less dependent on the hospital, and improves patient quality of life. This is especially important for HNC patients, who frequently have functional restrictions because of the location of their tumors and the effects of radiation therapy. However, careful adjustment of dosage, formulation, and adherence methods is necessary due to the distinct anatomical and physiological problems associated with HNC. Metronomic chemotherapy and TKIs, re the two main oral therapeutic treatments that have been investigated in both palliative and maintenance settings. Afatinib, a second-generation irreversible pan-ErbB inhibitor that blocks EGFR, HER2, and HER4, has become a viable oral alternative [79]. Apart from targeted therapy, metronomic oral chemotherapy (low-dose, frequent) has been extensively studied. Methotrexate (e.g., 15 mg/m² weekly) is typically used in conjunction with celecoxib (200 mg twice daily) as part of a metronomic regimen; in certain protocols [80]. Studies on advanced HNC have documented the anticancer effects of tegafur-uracil as a metronomic drug [81]. These oral regimens are especially appealing because they provide clinically significant benefits while being inexpensive, easily available, and more convenient for patients—particularly in low- and middle-income nations [82]. Moreover, oral morbidities related to the disease and therapy pose serious obstacles to oral medication delivery in head and neck cancer, as they can significantly reduce absorption, adherence, and tolerability. Radiation or chemoradiation-induced mucositis, which affects almost all patients receiving head and neck radiation and can be severe enough to require feeding tube placement and perhaps hospitalization, is one of the most significant obstacles [83]. Mucositis makes it very difficult to swallow oral medications since it causes ulceration, discomfort, and inflammation of the oral mucosa [84]. Oral intake is further complicated by swallowing difficulty (dysphagia) brought on by mucosal damage and fibrosis: Research indicates a significant inverse relationship between the degree of mucositis, xerostomia, and swallowing function in patients with HNC [85]. Delivering successful oral medication can be challenging due to the combination of these factors, which might affect drug adherence, bioavailability, and constant systemic exposure.

### *4.3.2 Intravenous drug delivery therapies in HNC*

Intravenous medication delivery is the main and most effective systemic therapy option in HNC, particularly in cases of both locally advanced and recurrent or metastatic. The IV route allows for quick systemic distribution, uniform plasma exposure, and direct clinical supervision during delivery because many common chemotherapeutic and biologic drugs used in HNC have poor oral bioavailability, high molecular weight, or require controlled dosage. When it comes to induction regimens, concomitant chemoradiotherapy, and palliative situations, intravenous chemotherapy is a key part of systemic treatment for HNC. It has been shown that adding docetaxel to cisplatin/5-FU boosts therapy efficacy in both metastatic and locally advanced illness, but also exacerbates hematologic toxicity (neutropenia) [86]. Platinum-based chemotherapy, cetuximab, and PD-1 inhibitors are highlighted as essential IV systemic modalities in current clinical practice guidelines, which also mention antibody-drug conjugates, innovative IV nanocarriers, and chemo-immunotherapy combos as active research topics [87].

In the treatment of head and neck cancer, oral and intravenous medication delivery methods complement one another. While intravenous treatment guarantees accurate dose and quick therapeutic action, particularly in advanced disease, oral medicines enhance patient convenience and long-term compliance. In order to maximize effectiveness and patient results, personalized therapy options increasingly incorporate both methods (**Figure 2**).

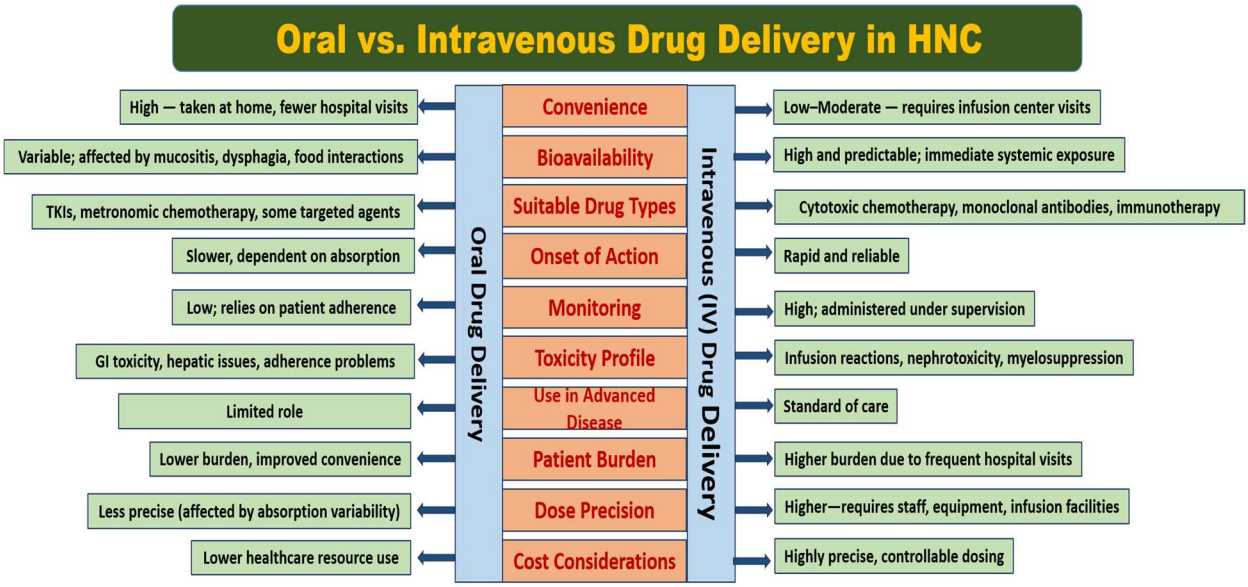


**Figure 2.** Comparative overview of oral and intravenous (IV) drug delivery systems in HNC.

## 5. Conclusion

The biochemical issue, epigenetic control, and targeted drug delivery of head and neck cancer present an intersection to clarify why a dual-focus, patient-centric approach to precision oncology is necessary. New data points to the fact that the systemic conditions like inflammation, malnutrition and metabolic imbalance play a crucial role in the drug response, the treatment tolerance and treatment outcome, which often determines the effectiveness of the advanced therapeutic programs. These determinants of the host and molecular targeting are therefore required to ensure maximum effect of treatment. The routine biochemical surveillance, consisting of such markers as C-reactive protein, serum albumin, and ferritin, must be incorporated into therapeutic trials in future clinical frameworks to make it possible to assess the nutritional and inflammatory conditions dynamically. Comparison of these parameters with the adverse events of the therapy, dose changes and the percentage of patients who complete the treatment will enable a more precise stratification of patients and individual treatment planning. Simultaneously, biocompatible and nutrient-sensitive drug delivery systems are under development, which provides a favourable perspective of increasing the drug bioavailability and reducing toxicity, especially in metabolically impaired patients.

Moreover, clinical investigations on drug efficacy and tolerability in malnourished and high-risk subgroups are critically needed to provide a transition between controlled

clinical trials and normal oncology practice. Incorporating nutrition and metabolic evaluation as an extension of oncologic care, not as an adjunct to it, will play a major role in enhancing treatment results. In conclusion, the forthcoming drug development and clinical guidelines in head and neck cancer should incorporate a combined design so that biochemical resistance corresponds to molecular accuracy to attain sustainable and proportional treatment achievement.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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## Ethical statement

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