Expanding the role of combined immunochemotherapy and immunoradiotherapy in the management of head and neck cancer (Review)

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Abstract. Immunotherapy has become one of the most promising approaches in tumor therapy, and there are numerous associated clinical trials in China. As an immunosuppressive tumor, head and neck squamous cell carcinoma (HNSCC) carries a high mutation burden, making immune checkpoint inhibitors promising candidates in this field due to their unique mechanism of action. The present review outlines a comprehensive multidisciplinary cancer treatment approach and elaborates on how combining immunochemotherapy and immunoradiotherapy guidelines could enhance clinical efficacy in patients with HNSCC. Furthermore, the present review explores the immunology of HNSCC, current immunotherapeutic strategies to enhance antitumor activity, ongoing clinical trials and the future direction of the current immune landscape in HNSCC. Advanced-stage HNSCC presents with a poor prognosis, low survival rates and minimal improvement in patient survival trends over time. Understanding the potential of immunotherapy and ways to combine it with surgery, chemotherapy and radiotherapy confers good prospects for the management of human papillomavirus (HPV)-positive HNSCC, as well as other HPV-positive malignancies. Understanding the immune system and its effect on HNSCC progression and metastasis will help to uncover novel biomarkers for the selection of patients and to enhance the efficacy of treatments. Further research on why current immune checkpoint inhibitors and targeted drugs are only effective for some patients in the clinic is needed; therefore, further research is required to improve the overall survival of affected patients.

Contents

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1. Introduction

Head and neck cancers are a group of malignancies that occur in various head and neck regions, including the oral cavity, throat, voice box and nasal cavity. Head and neck cancers account for ~4% of all cancer cases worldwide (1). The incidence varies globally, with higher rates in certain regions, such as Southeast Asia, where tobacco and betel nut use is prevalent (2). The primary risk factors for head and neck cancers include tobacco use (including smoking and smokeless forms) and alcohol consumption (3). Human papillomavirus (HPV)

infection, particularly HPV-16, is a significant risk factor for oropharyngeal cancer (4). Men are more commonly affected by head and neck cancers than women (5). The incidence increases with age, with most cases diagnosed in individuals >50 years (6). The specific sites affected by head and neck cancers include the oral cavity (including the tongue, gums and lips), pharynx (including the oropharynx and hypopharynx), larynx, nasal cavity and paranasal sinuses (7). Squamous cell carcinoma (SCC) is the most common histological type, accounting for most head and neck cancer cases. SCC accounts for 90-95% of all head and neck cancer cases (8). Other less common types include salivary gland tumors, lymphomas and sarcomas (9).

The prognosis for head and neck cancers depends on several factors, such as the stage of the disease at diagnosis, the tumor's location and the patient's overall health. Early detection and timely treatment significantly improve the chances of successful outcomes (10). Prevention and early detection through regular dental and medical check-ups, lifestyle modifications (avoiding tobacco use and excessive alcohol consumption) and vaccination against HPV (for oropharyngeal cancers) are essential in reducing the burden of head and neck cancers (11).

Head and neck cancer often presents a challenging and complicated situation, with low survival rates for advanced-stage patients and minor improvement in survival rate over time (12). Clinical treatment strategies include surgical procedures, chemotherapy, radiotherapy, immunotherapy and specific combinatorial approaches (13). Immunotherapy has received an increasing amount of attention and is considered the first line of treatment for patients with head and neck cancer (14). Clinical preliminaries of immune checkpoint inhibitors, monoclonal antibodies, adoptive T-cell therapy and chimeric antigen receptor (CAR) T-cell therapy show promising outcomes for head and neck cancer treatment (15). However, there is variation in patients with head and neck cancer; thus, combining immunotherapy with other treatment approaches such as surgery, chemotherapy and radiotherapy presents a significant clinical advantage in treating head and neck cancer (16). In addition, numerous adverse effects remain to be eliminated to optimize the clinical potentials of immunotherapy, including incidental effects, patient choice, selection of known biomarkers and the choice of novel immunotherapy (17). Immunotherapy has so far demonstrated high efficacy for managing intermittent and metastatic cancer (18). A better understanding of the immune system, and its influence on the progression and spread of head and neck cancer can lead to the discovery of new biomarkers. These biomarkers can be used to categorize patients into specific treatment plans, thereby conserving medical resources and ensuring timely and optimal treatment for each individual (19). Whilst the head and neck region exhibits significant anatomical variations in comparison to other parts of the body, there are several challenges in managing head and neck cancer, since most confer a poor prognosis (20). Clinically, head and neck cancer are challenging to treat with chemotherapy, radiotherapy and surgery, since metastasis is common in a number of patients and this cancer has a high chance of reoccurrence (21) (Fig. 1). Despite these challenges, immunotherapy shows significant therapeutic potential for patients with cancer, since immunotherapies can induce an immune response aiming to recognize and eliminate cancer for a while (22). Utilizing immunotherapy, chemotherapy, radiotherapy and surgery, alone or in combination, brings high efficacy in patients with head and neck cancer. Treatment efficacy in patients with head and neck cancer depends on whether the tumor is benign or malignant (23).

Head and neck SCC (HNSCC) has comparable etiologies, pathogenesis and therapeutic responses with other types of tumors (24). Neoplasm growth is favorable in organs lined with mucosa and in cells and tissues such as neuroendocrine cells, lymphoid tissue, minor salivary gland tissues and melanocytes. These cancers differ from the biology of HNSCC and have a different natural history (25). HNSCC manifests as a persistent sore throat, difficulty swallowing or a lump in the neck (26). By contrast, the symptoms of other types of cancer, such as lung cancer, may include persistent cough, shortness of breath or chest pain (27). Similarly, malignancies of the thyroid and major salivary gland act differently to HNSCC. Previously, head and neck cancer treatments were primarily limited to surgeons and radiation oncologists (28,29). However, advancements in medical knowledge and technology have expanded the range of specialists involved in managing this condition over time. Today, a multidisciplinary approach involves a team of healthcare professionals such as surgeons, radiation oncologists, medical oncologists, otolaryngologists, maxillofacial surgeons, speech and swallowing therapists, nutritionists and social workers (30). These specialists collaborate to provide comprehensive care, tailoring treatment plans to individual patient needs and improving outcomes for those affected by head and neck cancer (31). There have been significant advancements in surgery, radiotherapeutics, chemotherapy and immunotherapy as treatment approaches. In radiotherapy, the development of different fractionating schemes and intensity-modulated radiotherapy has enhanced the delivery and tolerance of radiation (32). Organ function conservation is improved through the advancement in conservative surgical procedures, including laryngeal prosthesis, laser surgery and hemilaryngectomy (33).

Chemotherapy is a significant component in the multimodality therapeutic strategies for advanced HNSCC, and the United States Food and Drug Administration (FDA) approval of various immunotherapies also brings hope to more patients with HNSCC (34).

The multidisciplinary approach aiming to treat HNSCC is unpredictable but is advancing. Several therapeutic approaches are outlined in the current review, representing significant achievements that can change the ideal treatment plan and results in patients with HNSCC. Immunotherapy represents a chance to improve the adequacy of conventional treatments. In fact, immunotherapy has significantly enhanced the therapeutic scene for patients with malignancy. Programmed cell death-ligand 1 (PD-L1) and programmed cell death protein-1 (PD-1) checkpoint inhibitors are the front lines of this clinical approach (35). The current review describes some new improvements in HNSCC, highlighting the efficacy of the use of immunotherapy combined with other therapies for improving the prognosis of HNSCC. It also outlines the current challenges and future perspectives for further research and clinical translation aiming to improve overall survival.

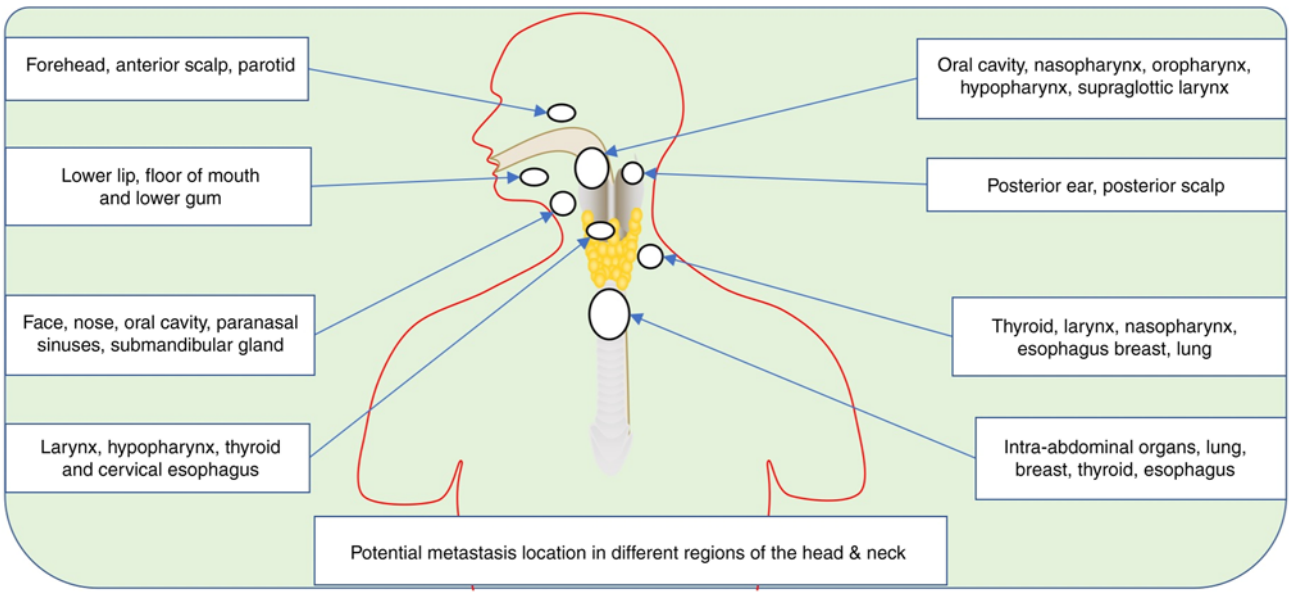

Figure 1. HNSCC development and metastasis. HNSCC originates from the mucosal epithelium of the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. Tobacco-related HNSCCs generate in the oral cavity, hypopharynx and larynx, while human papillomavirus-related HNSCCs generate from the palatine and lingual tonsils of the oropharynx. HNSCC, head and neck squamous cell carcinoma.

2. Anatomy of the head and neck, and clinical findings

The head and neck are classified into differential anatomical sections: Nasal-cavity, paranasal sinuses, oral cavity, pharynx and larynx (36). The pharynx comprises the nasopharynx, oropharynx and hypo-pharynx, as the larynx comprises the supraglottic, glottic and subglottic regions (37). Most patients present with variable features based on the anatomical location of the tumor (38). In most early cases, the patients will present symptoms that are difficult to diagnose just with a physical examination (Table I). Most HNSCC cases occur in cigarette smokers and alcohol consumers. The rate and duration of smoking and drinking increase the patient's chances of having oral cavity cancer (HNSCC) (7,39). Geographical location is also an influential factor for HNSCC; as frequently reported by the World Health Organization, exposure to pollution and some viral agents also increases the incidence of HNSCC (40). However, gene mutation and other genetic factors are also contributing agents for HNSCC (41), which require further research, since the mechanisms are not well understood.

3. Impact of HPV, Epstein-Barr virus (EBV), lifestyle and environment associated with head and neck cancer

HNSCC also affects a percentage of individuals without the typical risk factors for these neoplasms. Subjects with HNSCC who do not smoke and drink tend to be younger and have a primary neoplasm in the lingual or palatine tonsils (42). Within this category of patients, HPV is linked to HNSCC pathogenesis (5). HPV oncoproteins E6 and E7 inactivate tumor suppressor genes within the host cells, enhancing cell cycle control and suppressing programmed cell death based on the hypothesized cancer mechanism (43). Different types of cancers exhibit unique genetic and molecular attributes; at the same time, other factors like the tumor microenvironment and interactions with the immune system significantly contribute to cancer growth and progression (44). The oral cavity and the pharynx are the most common sites for HPV-related malignancies, and although the larynx is not one of them (larynx is primarily associated with other risk factors, such as tobacco and alcohol use, and exposure to environmental carcinogens), 85-90% of HPV-positive HNSCC is HPV-16 (45,46). It is unknown whether HPV and cigarettes or alcohol have any connection, and more research is required (47). Sexually transmitted diseases, such as human immunodeficiency virus infection, commonly spread through indiscriminate sexual partners and via oral and anal intercourse, and have all been linked to HPV-positive HNSCC (48). Increased alterations of genes previously implicated in the formation of HNSCC and exacerbated HPV-mediated carcinogenesis are caused by abnormal DNA repair and chromosomal destabilization, typical of this cancer (49). HNSCC with HPV appears to have a better prognosis than HNSCC without HPV (5). HPV-positive cancers appear to be highly radiosensitive, according to research (50). The lack of field cancerization and concomitant diseases, such as chronic obstructive pulmonary disease or cirrhosis, which influence the individual subject's overall prognosis, are potentially responsible for superior results (51). The discovery of HPV in HNSCC has both epidemiological and therapeutic implications, as individuals with HPV-positive malignancies are highly radiosensitive, thus helping doctors to choose individual patients for specific therapeutic approaches (50). The usage of HPV vaccines for cervical tumors might potentially help to prevent HPV-positive HNSCC (52). Poor oral health is also associated with HPV and can modify the oral microbiota (12).

Several risks for HNSCC are geographically, habitually and culturally prevalent, with smoking and alcoholism scoring among the high-risk variables globally (53). It is worth noting that abusers of both tobacco and alcohol have an up to 35 times higher increased risk of HNSCC compared with non-tobacco and alcohol users (54). Tumor of the oral cavity has been

Table I. Presenting signs and symptoms of head and neck cancer[a].

Location of tumor	Descriptions of anatomy	Clinical features	(Refs.)
Nasal cavity, paranasal sinuses	Includes the lips, the front two-thirds of the tongue, the gums, the lining inside the cheeks and lips, the floor of the mouth under the tongue, the hard palate and the small area of the gum behind the wisdom teeth.	Unilateral epistaxis, nasal obstruction	(193,194)
Nasopharyngeal	The paranasal sinuses are small hollow spaces in the bones of the head surrounding the nose. The nasal cavity is the hollow space inside the nose.	Nodal-neck metastasis	(195)
Throat (pharynx)	The pharynx is a hollow tube ~5 inches long that starts behind the nose and leads to the esophagus composed of the nasopharynx, the oropharynx and the hypopharynx.	Ulcers, with impaired speech and feeding	(196)
Laryngeal	The larynx is a short passageway formed by cartilage just below the pharynx in the neck. The larynx contains the vocal cords; it also has a small piece of tissue, called the epiglottis, which moves to cover the larynx to prevent food from entering the air passages.	Persistent hoarseness	(197)
Salivary glands	The major salivary glands are in the floor of the mouth and near the jawbone. The salivary glands produce saliva. Minor salivary glands are located throughout the mucous membranes of the mouth and throat.	Cervical adenopathy, dysphagia, dysphonia	(198)

[a]Most of the tumors are noticeable in the late stages, and in numerous cases, survival rate is poor, resulting from the high probability of metastasis.

linked to areca nut chewing, specifically a variety of customized combinations containing areca nut (*Areca catechu*; the carcinogen source), betel leaf (*Piper betle* leaf), slaked lime and tobacco, as well as spices commonly known as betel quid according to local custom (55). Oral cavity cancer is associated with the products of areca nut or betel quid consumption in India (the 1st and 4th most frequent neoplasm, respectively, in both sexes of the Indian population), Taiwan and several regions in China mainland (56). The high male/female ratios with HPV-negative HNSCC incidence indicate sex-specific patterning of modifiable risk behaviors, such as tobacco, smokeless tobacco, areca nut, betel quid and alcohol use (Fig. 2). The impact of electronic cigarettes on the risk of HNSCC is unclear and will only become apparent over the next few decades (57).

Carcinogenic air pollutants, such as organic and inorganic compounds, are also risk factors for HNSCC, particularly in developing nations/areas where air pollution is high, including China and other Asian and African countries (58). Other risk factors include age, improper dental hygiene and insufficient diet (59). Persistent HPV and EBV infections are recognized HNSCC etiological risk factors from the oropharynx and nasopharynx (60). The ratio of men to women is typically higher for oropharyngeal cancer, which is the most common site of HPV-associated HNSCC. Studies have reported a male-to-female ratio ranging from 2:1 to 4:1 for HPV-positive oropharyngeal cancer (61,62); this means that the incidence of HPV-positive oropharyngeal cancer is generally higher in men than in women (63). HPV infection resulting in HNSCC is mainly spread through oral intercourse, and the occurrence of HPV-positive HNSCC is on the rise, particularly in individuals without the HPV vaccine before exposure to HPV; in some cases, HNSCC is influenced by hereditary factors (64). Patients with Fanconi anemia, an uncommon genetic genealogical condition characterized by poor DNA repair (due to mutants in any of the 22 Fanconi anemia genes), have a 500-700 times higher risk of HNSCC, primarily oral malignancies (65). Although the reasons behind individuals with Fanconi anemia's predisposition for HNSCC are unknown, changes in Fanconi anemia pathway genes have a potential role (66).

Polymorphisms in genes implicated in carcinogen metabolism and immunity, such as interleukin-10 (IL-10, 1082A>G), cytotoxic T-lymphocyte associated protein 4 (rs231775 and rs4553808), cytochrome P450 1A1 (Ile462Val) and glutathione S-transferase μ1 (null polymorphism), are linked to an elevated risk, as demonstrated in a recent study (67). Thus, a weaker immune system and a decreased ability of carcinogen digestion may play a role in HNSCC. Carcinogens, such as tobacco smoke and alcohol, are known risk factors for HNSCC (68). The ability of the body to metabolize and detoxify these carcinogens can impact the likelihood of developing cancer (69). If

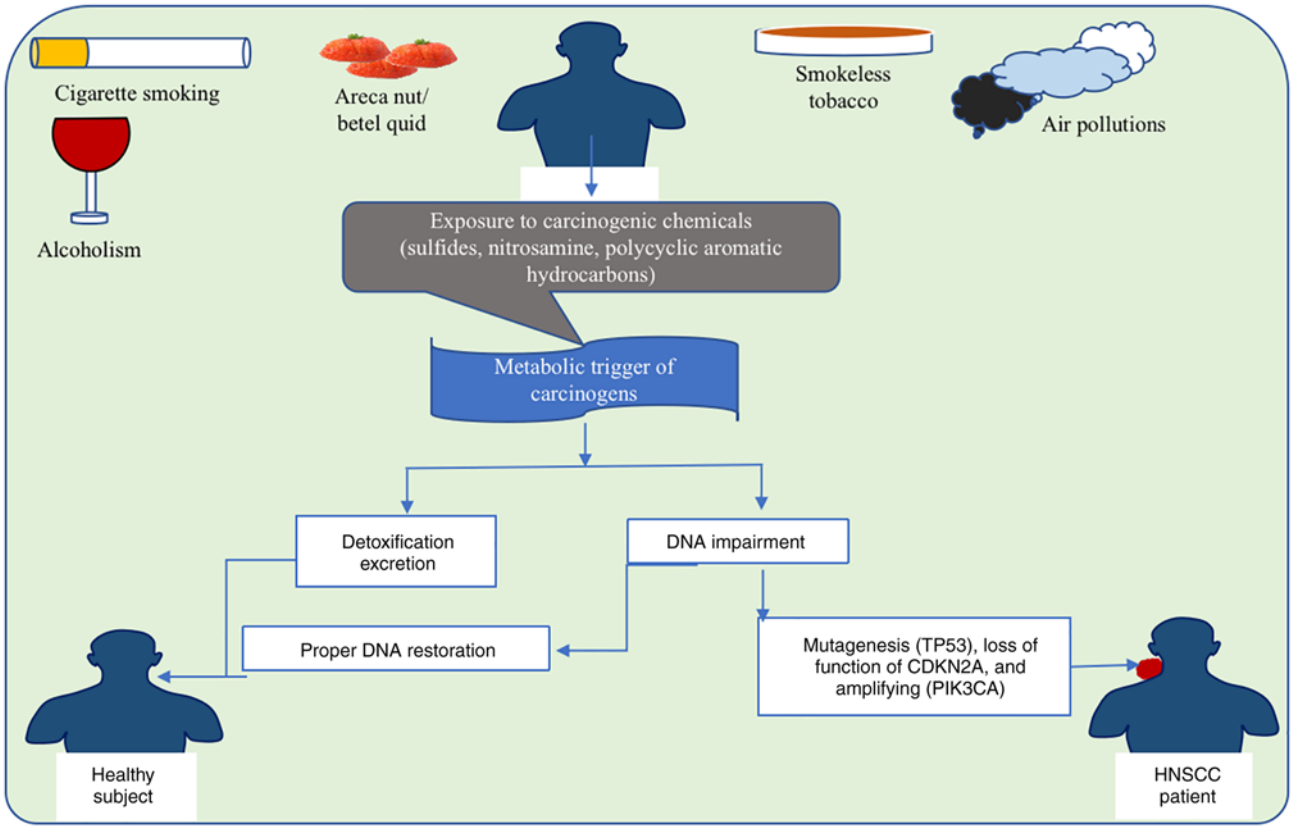

Figure 2. HNSCC growth influential factors. Tobacco products, betel quid and areca nut, as well as pollutants and alcoholic abuse are primary influential factors for the growth of HPV-negative HNSCC. Polycyclic aromatic hydrocarbons and nitrosamines can be found in large quantities in tobacco, which can be referred to as human carcinogens and can increase the risk of HNSCC. The upregulated expression of tumor suppressor genes TP53 encoding p53 and CDKN2A encoding p16INK4A result from the damaged DNA by carcinogens. In cases where the damaged DNA is not repaired promptly, or is repaired incorrectly by less accurate repair mechanisms, the genes involved in the PI3K-AKT-mTOR and RAS-MAPK pathways, which are associated with the progression of HNSCC and unfavorable outcomes in HPV-negative HNSCC, may be affected. HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; TP53, tumor protein p53; CDKN2A, cyclin-dependent kinase inhibitor 2A.

the body's digestion and detoxification processes are impaired, carcinogens may accumulate and cause damage to the cells of the head and neck region, potentially leading to the development of HNSCC (70). Reduced cigarette usage, proper oral care and universal HPV immunization could all contribute to lowering the universal HNSCC occurrence (71).

4.Tumor microenvironment (TME) and immunity

The TME in HNSCC is a heterogeneous mixture of tumor cells and stromal cells, which incorporate endothelial cells, cancer-associated fibroblasts (CAFs) and immune cells (72). Tumor cells and CAFs promote the production of growth factors, such as vascular endothelial growth factor (VEGF), which binds on endothelial cells, invigorating neo-vascularization and supplying oxygen and nutrients to the tumor (73). Consequently, endothelial cells release factors that help the endurance and self-reestablishment of circulatory immune cells (74). CAFs are vital in HNSCC maturation and are discriminated from typical fibroblasts by the abundant expression of α-smooth muscle actin (αSMA). CAFs release EGF, VEGF and hypoxia growth factor, interleukin 6 (IL-6), cytokines and chemokines that advance tumor cell development, angiogenesis and enrollment of immune defensive cells (75). Furthermore, CAFs are a significant cellular component within the TME, engaged with the degradation and regeneration of the extracellular matrix and the reinforcement of EGFs, VEGF and TGF-β matrix-embedded growth, which leads to further enhancement of tumor cell multiplication, angiogenesis and immunosuppression (76). Elevated αSMA levels in HNSCC tumors predict a poor prognosis; HNSCC tumors contain newly formed adrenergic neurons whose presence boosts tumor development (77). TP53 has diverse functions in neurons, including neuronal development, DNA damage response and neuroprotection (78). In HNSCC, TP53 alterations contribute to tumor development, progression and therapy resistance (79). Tumor-infiltrating lymphocytes (TILs) such as T cells, B cells and natural killer (NK) cells, as well as myeloid ancestry cells, including macrophages, neutrophils, dendritic cells and myeloid-derived suppressor cells (MDSCs), are the immune entities of HNSCC TME cells (80). Immune cells can invade HNSCC tumors under exceptional circumstances, for example in response to an inflammatory response, tumor antigen recognition, chemokine signals and tumor-induced angiogenesis, despite the fact that the infiltration composition depends on the tumor's anatomical location and its causative agent (81).

The response to therapy by HNSCC results from a specific immune phenotype; the most favorable prognosis of HNSCC is achieved with an increase in TIL level, which is reliant

upon the availability of antitumor responses, vs. those with immunosuppressive activities in the TIL population (82). The TME of most HNSCC tumors is profoundly immunosuppressive, and antitumor immunity in the TME is mediated mainly by T effector (T eff) cells and NK cells. By contrast, immune suppression and tumor cell growth are mediated by T regulatory (T reg) cells, MDSCs and macrophages (83). An increase in the survival of patients is based on $CD8^+$ T eff cells and NK cells in the TME (84). Paradoxically, T reg cells, MDSCs, neutrophils or macrophages increase and are associated with late-stage HNSCC (85). Most patients with HNSCC present with a variation in HPV-positive and HPV-negative tumors (86). HPV-positive tumors regularly have a more prominent presence of TILs compared with HPV-negative tumors (87). Patients with HPV-positive tumors and a number of TILs strongly respond to immunotherapy treatment. However, patients with HPV-positive tumors containing low content of TILs show survival rates close to those with HPV-negative HNSCC (47,88). The HNSCC TME milieu is rich in immunosuppressive components and cytokines that advance the enrolment or activity of MDSCs, T reg cells and macrophages, while hindering the antitumor effect of T eff and NK cells, IL-6, IL-10, VEGF and TGF-β (89). The HNSCC TME is rich in IL-10 and TGF-β, elevating macrophage polarization to an immunosuppressive phenotype (90). Furthermore, HNSCC tumors in significantly advanced stage cancer show upregulation of PD-L1, which weakens the cytolytic activity of T cells (60).

5. Therapeutic approaches for head and neck cancer

HSCC is one of the most immunosuppressive malignancies. Impaired immune-effector cell function, abnormal cytokine expression and increased T reg cell frequency in tumors and circulation characterizes HNSCC (91). In addition, the presence of T regs in patients with HNSCC characterized by high expression levels of immune checkpoint ligands such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) effectively downregulates the antitumor function of cytotoxic T cells (92). Cetuximab, an EGFR-specific monoclonal antibody used as an immunological intervention for locally progressive HNSCC at intermediate and high risk, shows promising results in patients with HNSCC (93). Combining radiation therapy for locally advanced HNSCCs and cytotoxic chemotherapy for recurrent/metastatic HNSCs together with immunotherapy improves survival (94). However, cetuximab, as a single agent, has limited effectiveness in the treatment of clinically treated advanced HNSCC and the response rate or clinical benefit rate of cetuximab as a standalone therapy is <15% (95). Therefore, numerous studies aim to explore combination treatment options to enhance the effectiveness (96). An attempt to use cetuximab plus radiation therapy in combination with ipilimumab, in a phase I clinical trial of CTLA-4 monoclonal antibody for locally advanced HNSCC (NCT01935921), showed impressive results. This study first explored radiotherapy plus dual-target immunity (cetuximab, ipilimumab) for locally progressive HNSCC (97). Regular cetuximab plus intensity modulated radiation therapy was administered at 5, 8, 11 and 14 weeks of treatment with ipilimumab (1 mg/kg). The method is not only safe but also curative; the 3-year disease-free survival and overall survival (OS) rates reached 72% [90% confidence interval (CI), 57-92] and 72% (90% CI, 56-93) respectively, with no dose-limiting toxicity (98). Head and neck malignancies are increasing, and >90% of them are SCCs (99).

Recently, immune checkpoint inhibitors targeted PD-1 and CTLA-4 have gained rapid development in the field of cancer therapy (100). The US FDA and the European Medicines Agency approved palivizumab and nivolumab for the first-line/second-line treatment of relapsed/metastatic HNSCC (101). However, >60% of patients with HNSCC are at stage III or IV; for locally advanced patients, the prognosis is still poor under the current multidisciplinary treatment model, with a 5-year OS rate of ~50% and the risk of local recurrence or metastasis of ~40% (102). Using immunotherapy as a neoadjuvant or perioperative treatment option for HNSCC to improve survival in patients in the early and middle stages is an excellent point for further research (103). p16 and p53 are closely linked to HPV and its role in the progression and prognosis of HNSCC (45). Various factors, such as tobacco smoking, alcohol abuse and pollutants, can influence the transformation of normal cells into tumor cells (104). Significant therapeutic advancements have been made in the treatment of HNSCC. In 2006, the FDA approved cetuximab as the first-line drug for recurrent and metastatic HNSCC, marking a significant milestone (105). Surgical procedures remain the primary option for removing non-metastasized oral cavity and oropharyngeal cancer (106).

Furthermore, the FDA has approved nivolumab and pembrolizumab for patients with platinum-refractory recurrent and metastatic HNSCC. Cetuximab, 5-fluorouracil (5-FU) and cisplatin have also received approval for treating patients with recurrent and metastatic HNSCC (107) (Fig. 3). Several therapeutic agents exist for head and neck cancer with significant therapeutic potential and efficacy; however, numerous patients cannot benefit from these therapeutic approaches in full as they are at a more advanced stage (108). When using immunotherapy as a monotherapy or in combination with chemotherapy, radiotherapy or surgery, a reasonable corrective improvement outcome can be achieved, improving the patient's life and prolonging the survival rate.

6. Immunotherapy for head and neck cancer

Immunotherapy has been one of the best therapeutic achievements against HNSCC for almost 10 years. This achievement can be attributed to immunosurveillance since the cancer cells need to invade the TME and become clinically notable. Subsequently the immune system fights against cancerous cells (109). The immune system patriates the optimal protective role against the development and metastasis of HNSCC. PD-1, which is primarily expressed on the surface of activated T cells, particularly $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells (110), acts as an immune checkpoint receptor crucial in regulating T-cell responses and sends negative feedback to abrogate the overactivation of T cells, thus preserving homeostasis and preventing autoimmunity (111). However, tumors can take advantage of this together with use of pre-existing inhibitory mechanisms preventing destruction by the immune cells (112). Checkpoint blockade by monoclonal antibodies senses the inhibitory signaling, which awakens T cells to respond to the

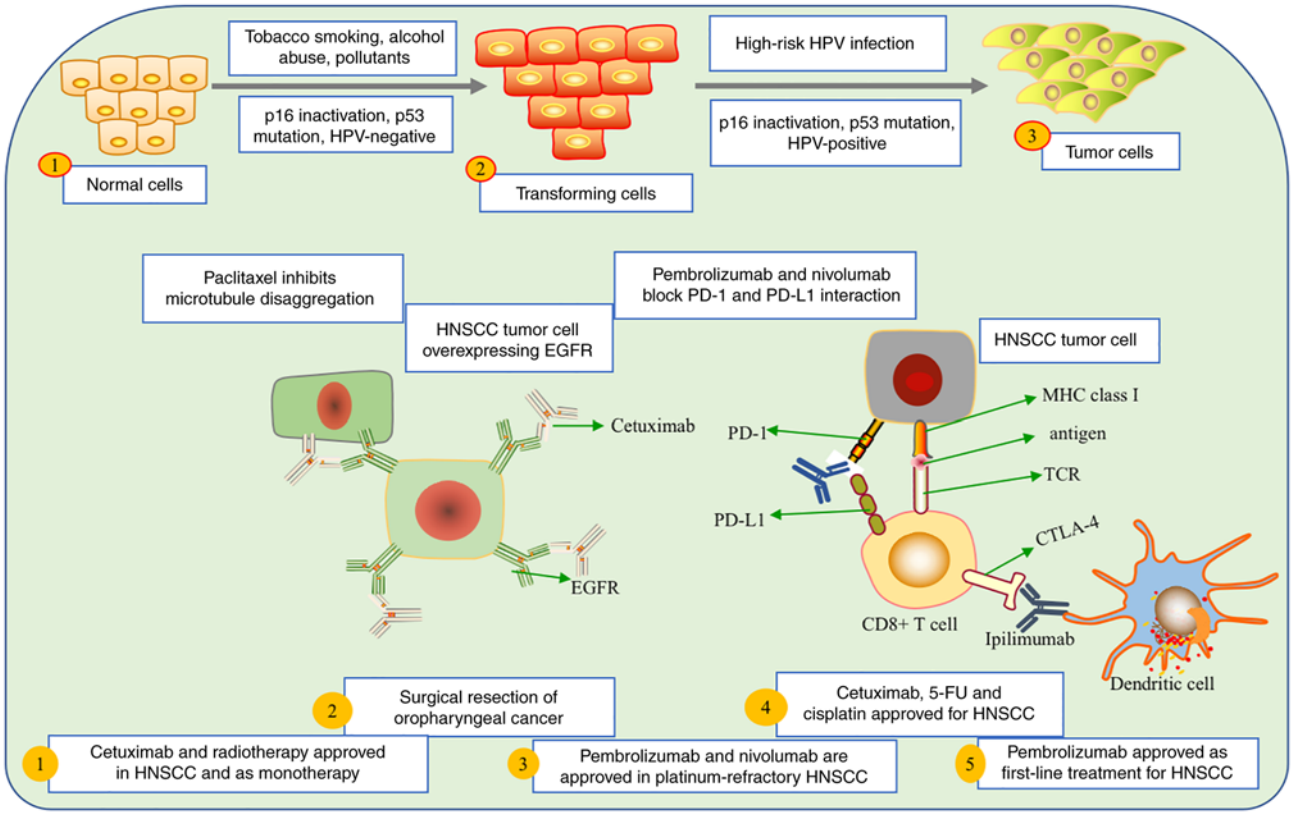

Figure 3. Stages of HNSCC and therapeutic advances for affected patients. Images with numbers circled in red illustrate a subset of HPV, tobacco smoking, alcohol abuse and pollutants associated with HNSCC progression and prognosis. In the lower image, numbers represent the following: 1, Cetuximab was the first drug approved by the FDA for use in patients with HNSCC. Cetuximab was approved in 2006 for use in patients with recurrent and metastatic HNSCC. 2, Surgical procedures were still seen as the best option in non-metastasized oral cavity cancer and robotic system for re-sectioning T1-T2 oropharyngeal cancer. 3, The FDA in November 2016 approved nivolumab and pembrolizumab for use in patients with platinum-refractory recurrent and metastatic HNSCC. 4, In 2006, Cetuximab, 5-FU and cisplatin were approved for patients with recurrent and metastatic HNSCC. 5, Pembrolizumab in August 2016, was approved as first-line treatment for patients with recurrent and metastatic HNSCC. 5-FU, 5-fluorouracil; CTLA-4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; TCR, T-cell receptor; MHC, major histocompatibility complex.

escaping tumors (113). Furthermore, some immune-related adverse events can be caused by aberrantly activated autoreactive T cells, among others, leading to inflammation in normal tissues (62). In addition, the neo-antigen peptides presented by the major histocompatibility complex activate the immune system to recognize tumor cells (114). Tumor-mutational burden (TMB) is connected with a mutation induced by smoking (signature 4 mutation-specific pattern of DNA damage caused by exposure to tobacco smoke carcinogens), which can be a response to PD-1 pathway blockade in both lung, and head and neck cancers (115). Nevertheless, some head and neck carcinomas, such as oropharyngeal carcinomas, result from viral agents such as HPV, leading to further comprehension of virally triggered immune-oncology mechanisms, which may further support the hypothesis that immunotherapy has the potential for optimal HNSCC treatment (116). Nivolumab and pembrolizumab have clinically demonstrated significant survival benefits in a number of patients (94). In addition, patients accepting anti-PD-1 agents appear not to show treatment-related adverse events (117). Furthermore, a phase I/II trial of durvalumab demonstrated a significant response for an antibody against PD-L1 in patients with HNSCC (118). The importance of the immune system in the progression and treatment of HNSCC has been appreciated for the possibility of utilizing the immune system for memorizing and eradicating cancer cells in preliminary clinical patients.

7. Interaction of biomarkers and immunotherapy

The immune phenotype of patients can be anticipated based on the expression of biomarkers (71); clinically, combination therapy in some specific patients induces an immunomodulatory response based on the morphology of the HNSCC (119). The efficacy of cancer immunotherapy depends on the immunological system's capacity to detect tumor cells and develop a cancer-selective response, with immunological memory possibly resulting in long-term cancer management (120). Primary resistance is a significant obstacle when the tumor appears, causing a negligible response to immunotherapeutic agents or when the tumor develops resistance, as well as when a tumor responds initially but subsequently develops resistance, thus decreasing the therapeutic efficacy of PD-L1-targeted treatment (121). An interaction exists between the immune system and the tumor's development; the adaptive immunological system takes advantage of both parties. The lack of immunogenic antigen proteins or their delivery to immunological systems are examples of T-cell-mediated resistance mechanisms (122). Other inhibitory cells, namely T reg cells,

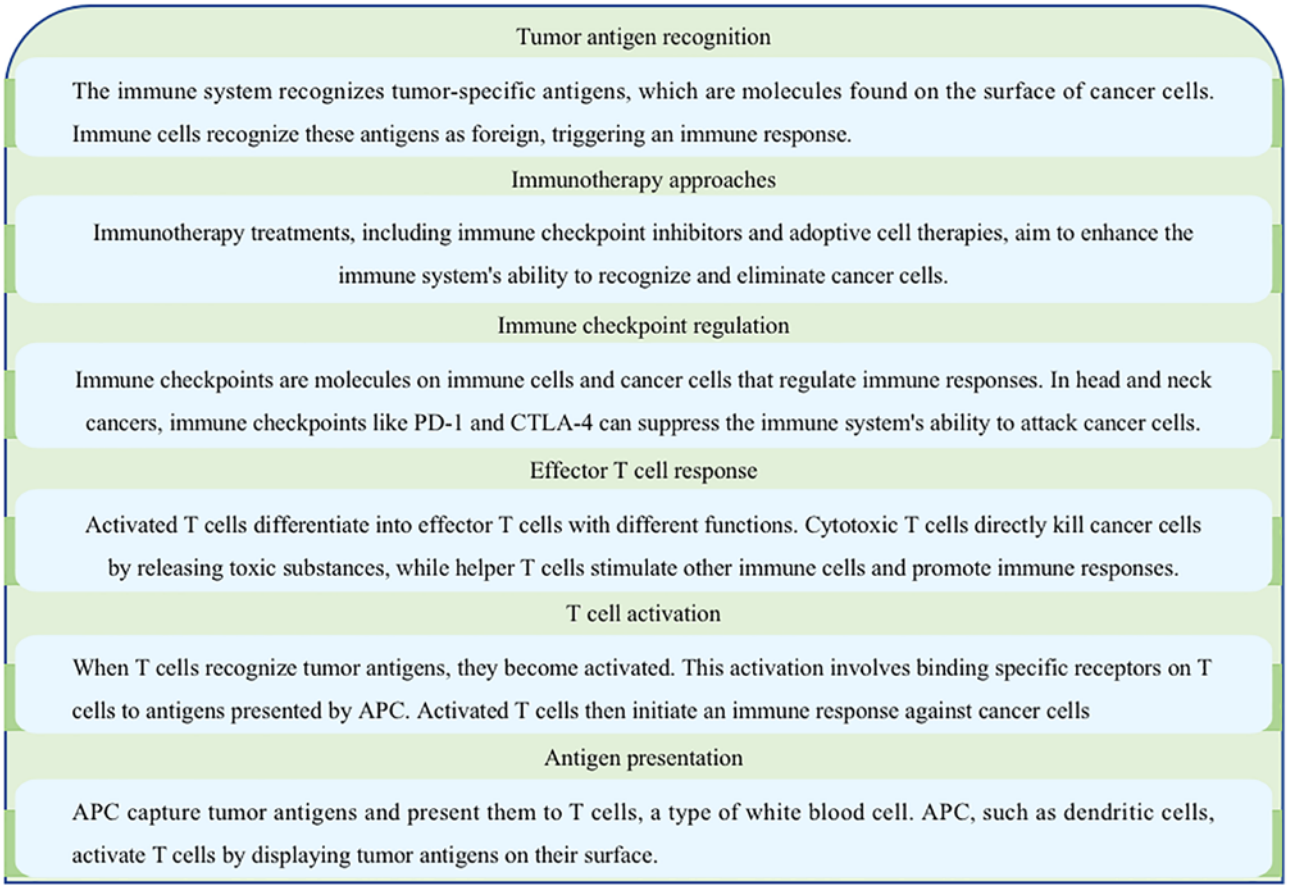

Figure 4. List of the various immune-related functions associated with HNSCC. The tumor-specific antigens, immune checkpoint inhibitors, such as PD-1 and CTLA-4, helper T cells, dendritic cells and activated T cells serve a significant role in developing and progressing head and neck cancer. Tumor-infiltrating lymphocytes, particularly T cells, are crucial for immune surveillance and anti-tumor responses. HNSCC exploits immune checkpoint pathways, like PD-1/PD-L1 and CTLA-4, to evade immune recognition. CTLA-4, cytotoxic T lymphocyte antigen 4; HNSCC, head and neck squamous cell carcinoma; NK, natural killer; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; APC, antigen-presenting cell.

MDSCs and tumor-associated macrophages, can hinder the function of cytotoxic T cells, and this inhibition is observed in cases where PD-L1 expression is linked to cancer development (123). Instead, cancer cell-mediated, tissue-selective or acquired microenvironment signal pathways might completely exclude T cells from the cancer cells (124).

The current knowledge on prognostic and predictive biomarkers must be improved in order to understand such a complicated system (125). The most frequently utilized technique to detect PD-L1 expression is immunohistochemistry; the expression of PD-L1 is used as a predictive marker for the response to specific treatments, particularly immunotherapies targeting the PD-1/PD-L1 pathway (35). An increased expression of PD-L1 is associated with a higher response to PD-1/PD-L1 blockade therapies (110). In addition, tumors with higher levels of PD-L1 expression may have more potential for interaction with PD-1 receptors on cytotoxic T cells, leading to T-cell exhaustion and reduced antitumor immune response (126). By blocking the interaction between PD-L1 and PD-1, immunotherapies can restore T-cell function and enhance antitumor activity as seen in some lung tumors and HNSCC (127). Every PD-L1-targeting antibody is accompanied by a diagnostic test specifically designed for it, and these diagnostic tests possess their own sensitivities and grading scales used to assess the level of PD-L1 expression in tumor samples, thus highlighting the importance of accurate diagnostic testing to determine the suitability of PD-L1-targeted therapies for individual patients (128). There is intra-tumoral heterogeneity, and expression may depend entirely on which metastatic location is affected and the changes in PD-L1 expression levels over time (63). HNSCC can metastasize to several region of the body, with higher levels of expression in the liver and adrenal gland compared with those in bone or brain metastases (129). TMB is a new surrogate biomarker for immunotherapy response that is still being investigated (130). TMB is linked to responsiveness to checkpoint blockade in tumors that have been shown to respond to immunotherapy, such as HNSCC, melanoma and mismatch repair-deficient cancers (131). TMB measurement is dynamic and changes depending on the platform used, similar to PD-L1 expression (132). TMB evaluation is not yet part of the clinical therapeutic strategy for lung tumors or HNSCC (133). The need for more potent prognostic and predictive biomarkers continues and will be critical in improving patient selection for the expanding number of treatments available (Fig. 4).

8. Immunotherapy and chemotherapy efficacy in HNSCC

Patients diagnosed with metastatic or advanced-stage HNSCC can benefit from a combined treatment approach involving

surgery and radiotherapy, which has demonstrated favorable outcomes, particularly in cases of nasopharyngeal cancer (134). However, other patients prefer a non-surgical approach; thus, the immune checkpoint inhibitor pembrolizumab, an IgG4 humanized antibody to PD-1, is considered the first-line treatment (135). A stage III preliminary study investigated the therapeutic benefits of pembrolizumab as a monotherapy or in combination with platinum-based chemotherapy drugs (5-FU or cisplatin) and cetuximab for patients with HNSCC, and demonstrated promising outcomes (136). Chemotherapy, in addition to pembrolizumab, further enhances efficacy, compared with chemotherapy combined with cetuximab, causing less toxicity to major organs (spleen, liver, heart, liver and kidney) (137). Pembrolizumab alone has low efficacy compared with combined chemotherapy and cetuximab for patients with HNSCC (62). Among patients characterized by the expression of the biomarker PD-L1, pembrolizumab monotherapy ensures a higher survival rate compared with chemotherapy combined with cetuximab (138). Nevertheless, combining chemotherapy with other cancer drugs shows a higher improvement rate in patients with HNSCC compared with monotherapy. Pembrolizumab and chemotherapy in patients with HNSCC demonstrate a superior efficacy as compared with pembrolizumab as a monotherapy (139). Hyper-progression is described in HPV-negative patients with local or regional tumor reoccurrence when immunotherapy is used without chemotherapy (140). Even though progression is related to a poor survival rate, most of the adverse events are manageable before the administration of chemotherapy (141). It is crucial to promptly adjust the treatment to enhance effectiveness while limiting immune-related adverse effects, such as pneumonitis, colitis and multiorgan injury (142). Patients who cannot receive first-line immunotherapy treatment may receive cetuximab combined with chemotherapy and platinum with 5-FU or paclitaxel (143).

In patients with cisplatin-resistant conditions, it is crucial to reconsider the expression of PD-1 in those with multiple concurrent cancers since PD-1 inhibitors can be used to overcome drug resistance in patients with HNSCC (144). When the prognosis for survival is not optimal, PD-1 inhibition can be an option for patients irrespective of the state of autoimmunity, which is worsened by immune checkpoint inhibitors in patients with cisplatin-refractory disease (145). PD-1 inhibition can improve survival with optimal efficacy in patients with HNSCC compared with the use of nivolumab or pembrolizumab monotherapy in patients with cisplatin-refractory disease (146). An initial clinical study reported on new immunotherapies for patients with metastatic or recurrent HNSCC (147), and the investigation of combined immuno-chemotherapy is ongoing (Fig. 3).

9. Surgery, radiotherapy and chemotherapy in HNSCC

Surgery, radiotherapy and chemotherapy are considered the best therapeutic options for HNSCC, with the principal purpose being to free the patients from cancer and prevent reoccurrence (84). In most patients with oral cavity cancer, surgical procedures are most likely to be the best option, whilst radiotherapy is considered the best option for patients with pharyngeal and laryngeal cancers (148). Advances in invasive resection, such as transoral automated robotic surgery or laser resection and larynx-saving partial laryngectomy, as well as advanced reconstructive procedures, and improved knowledge of the signs indicating the need for essential surgical management of patients with head and neck cancer have been broadened (149). Unexpected metastases noticed in draining cervical lymph nodes in some patients with small, intrusive tumors demand the use of dissection to improve survival (150). In case of failure of therapy after the use of a single methodology, radiotherapy or surgical procedure, the use of a different elective methodology offers a higher probability of success (151). Postoperative radiotherapy or chemoradiotherapy can ensure extended survival and minimize the risk of tumor recurrence for advanced tumors or those that have spread to nearby lymph nodes (152).

10. Immune checkpoint inhibitors and radiotherapy in HNSCC

Immune checkpoint inhibitors are being examined in preliminary studies in the therapeutic setting and in combination with other treatment modalities (153). Radiotherapy can positively affect cancerous cells and tissues by enhancing antitumor immune reactions (98). When immunotherapy is combined with radiotherapy, radiotherapy may improve the impact of immunotherapy by advancing the release of cytokines and tumor-associated antigens (154,155). Durvalumab in preclinical trials after chemoradiotherapy in patients with stage III HNSCC increases the survival rate when combined with chemoradiotherapy monotherapy (156). Numerous stage I/II preliminary studies on locoregionally progressed HNSCC are exploring a combinatorial approach, adding anti-PD-l antibodies to chemoradiotherapy (157). The potential of combining immunotherapy and radiotherapy in HNSCC is not well known, thus further investigation into the combination of radiotherapy with immunotherapy approaches is required.

11. Prognosis of combining immunochemotherapy and immunoradiotherapy for head and neck cancer

Numerous preliminary studies are currently assessing combinatorial treatments, including immune checkpoint inhibitors, therapeutic vaccines, co-stimulatory agonists and cytotoxic agents (158). Combinations of anti-CTLA-4 and anti-PD-1 antibodies show a synergistic effect in patients with melanoma and are currently being tested in patients with stage III HNSCC (156). The anti-CTLA-4 antibody tremelimumab in combination with the anti-PD-L1 antibody durvalumab in patients with metastatic HNSCC demonstrated an increased efficacy compared with either tremelimumab or durvalumab monotherapy (159). Numerous antibodies have additionally been scrutinized in stage I/II preliminary studies for patients with HNSCC (160). Furthermore, laherparepvec, in combination with cisplatin and radiotherapy, showed an increase in survival rate (161,162). A phase II study on the combination of nivolumab with the synthetic long-peptide HPV-16 vaccine demonstrated promising outcomes, with a superior response compared with that of anti-PD-I treatment alone, thus supporting the need of further investigation on the use of combinatorial immunotherapy for higher clinical efficacy.

Combining immunochemotherapy and immunoradiotherapy for head and neck cancer can improve prognosis and treatment outcomes. This approach uses chemotherapy and radiotherapy to enhance the immune response against cancer cells (163). Chemotherapy aims to destroy cancer cells throughout the body and reduce the size of tumors; it can also help sensitize the cancer cells to the effects of radiotherapy (164). Radiotherapy targets specific areas where the tumor is located, using high-energy radiation to destroy cancer cells (165). Combining these treatments with immunotherapy, which activates the body's immune system to recognize and attack cancer cells, has a synergistic effect (104). Immunotherapy helps in enhancing the immune response, making it more effective in recognizing and eliminating cancer cells (166). However, the prognosis of combining immunochemotherapy and immunoradiotherapy for head and neck cancer can vary depending on several factors, such as the stage and type of cancer, the overall health of the patient and the individual response to treatment (167). Clinical trials and ongoing research are essential for evaluating the effectiveness of these combined approaches and determining their impact on long-term prognosis.

12. Application of CAR T-cell therapy in HNSCC

CAR T-cell therapy involves modifying a patient's immune cells, particularly T cells, by introducing a synthetic receptor called CAR onto their surface (168). This receptor empowers T cells to recognize and bind to specific proteins known as antigens in cancer cells, resulting in their destruction. CAR T-cell treatment offers several advantages in addressing head and neck cancer (169). Firstly, these tumors often overexpress specific antigens such as EGFR or HER2, which can be targeted by CAR T cells (170). By selectively attacking cancer cells and sparing normal cells, CAR T cells reduce the risk of off-target effects. Secondly, CAR T-cell therapy can provide long-term antitumor benefits (171). Once the modified CAR T cells are introduced into the patient, they have the potential to persist and continuously identify and eliminate cancer cells (172). This sustained response is particularly beneficial for treating recurrent or metastatic head and neck malignancies that are challenging to address using conventional therapies (169). For instance, a preclinical study has demonstrated the effectiveness of CAR T cells targeting EGFRVIII, a type of EGFR widely expressed in head and neck malignancies (173).

Furthermore, clinical studies focusing on CAR T-cell treatment targeting HER2 have shown positive outcomes, with some patients experiencing significant tumor shrinkage and extended survival (170). However, it is essential to note that there are still obstacles to overcome in CAR T-cell therapy for head and neck cancer. The hostile tumor microenvironment poses a significant barrier, hindering T-cell activity and infiltration into the tumor (174). Combination therapies with immune checkpoint inhibitors or cytokine injections are being explored to enhance T-cell persistence and resistance to the immunosuppressive tumor environment (168). Another concern is the potential toxicity associated with CAR T-cell treatment, such as cytokine release syndrome and neurotoxicity (175). These systemic inflammatory responses can range from mild symptoms to life-threatening complications following CAR T-cell infusion (176). Efforts are underway to improve patient selection, dosing strategies and supportive care measures to better understand and manage these toxicities (176). Ongoing research and clinical trials provide valuable insights into optimizing the effectiveness and safety of CAR T-cell therapy (177). With further advancements and refinements, CAR T-cell therapy has the potential to become an essential addition to the treatment options available for head and neck cancer, offering new hope for patients facing this challenging disease.

13. Future investigations and conclusion

Several cancer therapies exist, the most recent being cancer immunotherapy, which significantly improves cancer treatment. Regardless of the achievements in cancer immunotherapy, the response in patients is regularly limited and not long-lasting (178). This is caused by multiple tumor-mediated immune escape mechanisms. The head and neck malignant growth rate changes across nations depending on hazardous factors, including alcohol and tobacco utilization and the comorbidity with HPV infection (179,180). Tumors positive for HPV overexpress the viral E6 and E7 antigens, which can be recognized by the immune system, thus stimulating an immune response (181). Current investigations suggest that the T cells responsible for the reoccurrence in HPV-positive tumors do not perceive these viral antigens but tumor neo-antigens or germline antigens (182). Promising antitumor viability in a murine HPV-16 E7 antigen-expressing tumor model, utilizing various combinations of E7 peptide antibodies, has been reported (183). This restorative adequacy can essentially be upgraded by combining PI3K-AKT pathway inhibitors with PD-1, PD-L1 and CTLA-4, and tumor necrosis factor (TNF) receptor superfamily member 4 (OX-40) and TNF receptor family-related protein TNF receptor superfamily member 18 (GITR) (184).

Combining various therapeutic approaches gives patients with HPV-positive head and neck cancer a promising outcome. Regardless of the clinical advantage of agents utilizing the synergy between PD-1 and PD-L1, most patients do not benefit from this treatment (185). T-cell agonist antibodies targeting GITR and OX-40 have entered preliminary clinical studies, and promising outcomes in preclinical mouse models anticipate clinical utilization (123,186,187). A few clinical preliminary studies are testing the efficacy of cancer immunotherapy in head and neck tumors (126,188).

Whilst immunotherapy has shown promising results, the high development, production and administration costs contribute to its expensive price tag. The high cost of immunotherapy can limit access for patients who may benefit from this treatment (107). It is a complex issue involving several factors, such as research and development expenses, manufacturing costs and ongoing clinical trials. Efforts are being made to address this issue (189). Some countries have implemented healthcare policies to make immunotherapy more affordable and accessible (190). Additionally, ongoing research and advancements in medical technology may lead to more cost-effective approaches to immunotherapy in the future.

Numerous researchers are examining the preclinical adequacy of new combinations while interpreting the specific mechanism of different treatments. There is promising

potential in consolidating various therapeutic agents, including immunotherapy, chemotherapy and radiotherapy (191). Further understanding of the correlations among multiple therapies is needed, and the current review outlines how researchers can proceed in the future. It is also essential to evaluate the adequacy of various therapies before combining different immunotherapeutic agents (192). Finally, immunotherapy has shown a high efficacy for aerodigestive malignancies and has paved the way for an optimal methodology aiming at a novel therapeutic approach (104). However, despite the success, further efforts are needed to improve the clinical efficacy in patients with challenging HNSCC.

In conclusion, enhancing immunochemotherapy and immunoradiotherapy for head and neck cancer is an active research and development area. Combining these treatment modalities aims to improve the effectiveness of cancer treatment by utilizing the body's immune system to target cancer cells. One approach involves using immune checkpoint inhibitors, drugs that help unleash the immune system to attack cancer cells. These inhibitors, such as pembrolizumab or nivolumab, can be combined with chemotherapy or radiation therapy to enhance the anticancer immune response. Current research focuses on identifying novel immunotherapeutic targets specific to head and neck cancer. By understanding the molecular characteristics of tumors, researchers hope to develop personalized treatment approaches that can stimulate the immune system to recognize and destroy cancer cells more effectively. It is important to note that specific treatment plans depend on individual patients and should be discussed with a healthcare professional. Clinical trials and advancements in this field continue to evolve, offering potential improvements in immunochemotherapy and immunoradiotherapy for patients with head and neck cancer.

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Authors' contributions

CW was responsible for conceptualization, and writing, RC and XL for conceptualization, writing and reviewing, QF and MQ for conceptualization, figure generation and reviewing. SAUS and TAM were responsible for writing, reviewing and editing. OJ was responsible for the study concept and design, draft manuscript preparation, and analysis and interpretation. Data authentication is not applicable. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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