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Current Concepts in Chemotherapy for Head and Neck Cancer

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide, with 700,000 cases diagnosed per year.¹ Although there have been advances in multimodality therapy, the overall 5-year survival rate remains approximately 40% to 50%.^{2–5} This review focuses on systemic treatments for HNSCC, including the evidence for current standards of care and promising strategies under development.

EPIDEMIOLOGY

Placing systemic treatment paradigms into context requires briefly reviewing the 2 dominant causes of HNSCC, environmental carcinogenesis and human papillomavirus (HPV). Mutagenic exposure to tobacco, alcohol, or the areca nut (betel quid) is the major cause of environmental carcinogenesis leading to HNSCC.⁶ In addition to direct individual exposure to carcinogens, distal societal conditions that result in exposure to second-hand smoke, pollution, and pestilence also contribute to risk. With both proximal and distal risk factors for environmental HNSCC associated with low socioeconomic status, HNSCC presents a substantial burden in developing countries. In the United States, there has been a decrease in overall tobacco use, which has led to a corresponding decrease in the incidence of environmental HNSCC. The risk of environmental HNSCC increases with increasing age, with a median age at diagnosis of 66 years.⁷

HPV is now recognized as a dominant cause and a critical determinant of prognosis in HNSCC arising in the oropharynx.⁸ Over the past 3 decades, both the incidence and overall

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survival (OS) of patients with oropharyngeal squamous cell carcinoma (OPSCC) have increased. Both phenomena are associated with an emerging epidemic of HPV-driven OPSCC, where favorable biology results in improved response to conventional therapies, including chemotherapy and radiation, relative to environmental or HPV-negative HNSCC.⁹ HPV, a member of the *Papillomaviridae* family, is a double-stranded DNA virus with more than 100 characterized genotypes. HPV genotype-16 is trophic for the lymphoid-rich oropharyngeal epithelium and is isolated from more than 90% of OPSCC specimens.¹⁰ In the United States, population registry data confirmed the epidemic rise in the proportion of OPSCC cases infected with HPV from 16% in 1984 to 72% in 2004.⁸ The median age at diagnosis for patients with HPV-associated OPSCC at 58 years is lower than those with environmental HNSCC.⁷

Because patients with HNSCC that is caused by environmental carcinogenesis have a poor prognosis compared with those with disease caused strictly by HPV who have a good prognosis, current strategies to develop therapy differ between the 2 etiologic settings. Specifically, for patients with HPV-negative (environmental) HNSCC, clinical trials are designed according to principles of intensifying treatment, whereas for patients with HPV-positive disease and with no or minimal past exposure to tobacco, clinical trials are designed according to principles of deintensifying treatment, with the rationale of reducing late toxicities yet maintaining excellent cure rates.

SYSTEMIC THERAPY IN PREVIOUSLY UNTREATED, LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

Locally advanced HNSCC is defined as stage III or higher in accordance with AJCC version 7. Thus, disease in patients with a primary tumor stage of T3 or higher and/or a regional nodal stage of N2 or higher is considered locally advanced. Approximately half of patients with PULA are treated with primary surgery and half are treated with primary, definitive radiation therapy (RT).

Primary Surgery

For patients with HPV-negative, locally advanced disease and pathologic high-risk features, recurrence rates after surgery alone are high. Therefore, postoperative treatment strategies have been actively investigated for several decades. The first intensification strategy in the adjuvant, pathologic high-risk setting evaluated the addition of concurrent cisplatin to adjuvant RT (Table 1). Radiation Therapy Oncology Group (RTOG) 95-01 and European Organisation for Research and Treatment of Cancer (EORTC) 22931 are 2 phase III randomized trials, which compared postoperative RT with or without concurrent cisplatin-based chemotherapy in patients with high-risk postoperative HNSCC.^{11,12} Although the trials were conducted in the era before HPV was recognized as an emerging cause of HNSCC, a majority of patients in these trials had nonoropharyngeal primary tumors that were presumably HPV-negative. These 2 randomized trials yielded positive results for their respective endpoints. Both studies used the same cisplatin schedule (100 mg/m² on days 1, 22, and 43 during RT). The 2 studies had slightly different inclusion criteria. For RTOG 95-01, pathologic high risk was defined as 2 or more metastatic lymph nodes, the presence of

extracapsular nodal extension (ENE), or positive surgical margins. For EORTC 22931, inclusion criteria were broader and included ENE, positive surgical margins, perineural invasion (PNI), lymphovascular invasion, and oral cavity or oropharyngeal primary cancers with level IV or level V lymph nodes. The EORTC trial enrolled 334 patients and demonstrated a benefit in local-regional disease control, disease-free survival (DFS) (primary endpoint), and OS for patients receiving cisplatin chemotherapy concurrent with RT. The RTOG trial enrolled 459 patients and revealed a benefit in local-regional disease control (primary endpoint) but not OS with the addition of cisplatin. In both trials, patients who received cisplatin had greater acute and overall toxicity.

To identify the patients most likely to benefit from such intense treatment, the investigators of both studies collaborated to perform a retrospective joint analysis of the 2 trials.¹³ The goal was to define the pathologic high-risk features associated with differential benefit from cisplatin. ENE and microscopically involved surgical margins were identified as the 2 pathologic factors most strongly associated with DFS and OS. Therefore, the investigators recommended the addition of concomitant high-dose cisplatin to postoperative RT in patients with either or both of these pathologic findings and who were medically fit enough to tolerate the added modality. Patients with other risk factors traditionally associated with high risk, such as 2 or more nodes, PNI, vascular tumor embolism, and clinically enlarged level IV/V lymph nodes secondary to oral cavity or oropharyngeal primary tumors, did not show benefit from the addition of chemotherapy—although this retrospective analysis was underpowered and could not rule out a small benefit in this population. Long-term follow-up results from both studies were published in 2012, confirming DFS and OS advantages in the subpopulation of patients with ENE or microscopic-positive margins.¹²

Concurrent cisplatin-radiation therapy is now the standard of care in patients with pathologic high-risk HNSCC. Cisplatin, however, exacerbates the acute toxicities of mucositis and dermatitis and is accompanied by significant systemic toxicity, including nausea and vomiting, neutropenia, kidney damage, peripheral neuropathy, tinnitus, and hearing loss. A substantial number of patients with HNSCC do not tolerate and cannot successfully complete the regimen of 100 mg/m² cisplatin every 3 weeks during radiation. Alternative strategies for radiation sensitization in the pathologic high-risk group are under investigation. One promising option involves the incorporation of molecular targeting agents, such as cetuximab, an IgG1 human-murine monoclonal antibody against the epidermal growth factor receptor (EGFR). After a phase III trial data demonstrated improved survival for radiation and cetuximab combined in the definitive treatment setting,^{14–16} developmental clinical trials for RT combined with cetuximab in the postoperative setting were pursued. RTOG 0234, a phase II, noncomparative, randomized trial, studied the use of concurrent chemoradiation therapy (CRT) and cetuximab in the adjuvant treatment of patients with pathologic high-risk HNSCC. Both HPV-positive and HPV-negative patients were included. Patients were randomly assigned to 60-Gy radiation with cetuximab once per week plus either cisplatin 30 mg/m²/wk or docetaxel 15 mg/m²/wk. The docetaxel-cetuximab regimen showed a favorable outcome with improved DFS and OS compared with historical control, warranting further investigation in high-risk, HPV-negative patients. This adjuvant strategy is now moving forward in a phase II/III trial (RTOG 1216) evaluating the adjuvant regimen of 60 Gy RT plus cisplatin versus RT combined with 1 of 2 docetaxel-

based experimental arms: docetaxel alone or the combination of docetaxel and cetuximab. On completion of phase II, the least favorable doce-taxel arm will be dropped and the most favorable will advance to phase III testing against cisplatin-RT. This trial will determine whether docetaxel alone is as effective as docetaxel and cetuximab combined and whether either taxane-based regimen is more effective than cisplatin monotherapy in high-risk, HPV-negative HNSCC. A positive outcome would support a new standard of care with a noncisplatin regimen in the postoperative setting.

A second trial in the high-risk, HPV-negative, adjuvant setting is NRG HN003, a phase I and expansion cohort study of adjuvant cisplatin, intensity-modulated RT, and pembrolizumab, a monoclonal antibody against programmed death receptor-1 (PD1). Pembrolizumab was the first immunotherapy approved by the US Food and Drug Administration (FDA) for the treatment of recurrent, metastatic, platinum-refractory HNSCC in 2016. Because of the association of HNSCC with a suppressive immune microenvironment, as well as the recognition of up-regulated PD1 with RT, the addition of immunotherapy to a CRT regimen has advanced in both adjuvant and definitive settings. The purpose of NRG HN003 is to investigate the safety of adding pembrolizumab to postoperative cisplatin-RT, setting the stage for a phase III randomized controlled trial against standard cisplatin-RT.

Although adjuvant cisplatin-RT is viewed as a standard of care for patients with pathologic high-risk HNSCC, the DFS and OS of patients with perineural or vascular invasion, 2 or more involved lymph nodes, or T3 and T4 tumors remain unsatisfactory. Such patients at pathologic intermediate risk and are commonly treated with postoperative RT alone. Intermediate-risk patients are currently under study in clinical trials separate from those of patients at pathologic high risk. RTOG 0920 trial is a landmark phase III randomized trial comparing RT alone versus RT plus cetuximab in patients with intermediate-risk disease.

Minimally Invasive Transoral Surgery

Traditional surgical approaches in the treatment of oropharyngeal cancer can result in morbidity with poor functional and cosmetic outcomes.¹⁷ Recent technological advancements have led to less invasive approaches, including transoral robotic surgery (TORS). TORS can offer better functional outcomes compared with mandibulectomy.^{18,19} Some studies suggest that TORS may improve rates of margin-negative mucosal resections, potentially reducing the need for adjuvant chemotherapy in addition to RT.¹⁹ Because of the epidemic of HPV-related OPSCC, a majority of TORS resections are performed for patients with HPV-positive disease. The recognition of a superior prognosis in this population raised the question whether the high-risk pathologic features first identified in HPV-negative disease warrant the use of adjuvant cisplatin-RT compared with a deintensified approach.

ECOG 3311 was designed to explore the combination of TORS and risk-based, deintensified adjuvant RT in patients with clinical T1-T2, N0-N1, HPV-associated OPSCC. Patients are stratified into 3 risk groups. Patients in the low-risk group (negative margins, 0–1 involved nodes, no ENE) do not receive any adjuvant treatment. Patients in the intermediate-risk group with negative margins, less than or equal to 1 mm ENE, or 2 to 4 involved nodes are randomized either to standard adjuvant RT at a dose of 60 Gy or to a deescalated dose of 50 Gy. High-risk patients with positive margins, greater than 1 mm ENE, or greater than or

equal to 4 involved LN, receive 66 Gy with concurrent weekly cisplatin. Results of the study are expected to determine more optimal treatment of patients with HPV-positive OPSCC.

Definitive Radiation Therapy

Intensification strategies that add systemic therapy to definitive RT in patients with PULA HNSCC have been under investigation since the 1980s. The Head and Neck Intergroup conducted a phase III randomized trial to test the benefit of adding chemotherapy to RT in patients with unresectable HNSCC²⁰; 295 patients with unresectable stages III-IV HNSCC were randomly assigned to RT alone, RT with concurrent bolus cisplatin 100 mg/m² every 3 weeks, or a split course of single daily fractionated RT and 3 cycles of concurrent infusional fluorouracil and bolus cisplatin chemotherapy. OS and DFS were improved with the addition of concurrent high-dose, single-agent cisplatin to conventional single daily fractionated RT, although cisplatin also increased toxicity. This study established definitive cisplatin-RT as the standard of care for locally advanced HNSCC. This trial was accrued from 1992 to 1999, before the recognition of HPV as a cause of OPSCC, thus cisplatin-RT became the de facto standard without regard to HPV status.

Due to the high toxicity profile of cisplatin, which is often prohibitive for HNSCC patients with a high burden of comorbidities, other systemic therapies have been investigated for intensification. With the advent of molecularly targeted therapy against EGFR, near universally overexpressed in HNSCC, Bonner and colleagues¹⁵ conducted a phase III trial to evaluate cetuximab with RT versus RT alone. Poor surgical candidates with locally advanced SCC of the oropharynx, hypopharynx, and larynx were randomly assigned to RT and concomitant weekly cetuximab (211 patients) versus RT alone (213 patients). The primary endpoint of the trial was duration of locoregional control (LRC). Secondary endpoints included OS, progression-free survival (PFS), overall response rate, and safety. The study showed that concomitant treatment with cetuximab improved LRC and decreased mortality versus RT alone. Furthermore, this study showed no evidence that cetuximab increased the rate of greater than or equal to grade 3 mucositis or dysphagia, no evidence of an increased rate of late effects, and no evidence of a worsening of quality of life relative to RT alone. Updated results with 5-year survival were recently reported and demonstrated 5-year survival of 45.6% in the cetuximab plus RT group vs 36.4% in the RT alone group.¹⁴ HPV status was retrospectively obtained by p16 immunohistochemistry in the OPSCC subgroup. Although HPV was prognostic of better oncologic outcomes among HPV-positive vs HPV-negative patients, the addition of cetuximab improved LRC, PFS, and OS in both subgroups, indicating that cetuximab-RT is an appropriate standard in both clinical settings.²¹

Deintensification Strategies

Because patients with HPV-associated OPSCC have a better prognosis than patients with HPV-negative HNSCC, irrespective of treatment modality, and because current treatment paradigms were developed during the era of HPV-negative disease, an important research question has emerged: whether treatment can be deintensified in the HPV-positive cohort to minimize late toxicity without compromising excellent cure rates. HPV status now serves as a biomarker for clinical risk stratification, identifying the appropriate populations for deintensification approaches. The first such classifier was developed by Ang and colleagues,

²² and retrospectively evaluated HPV-status among the OPSCC subgroup of the RTOG 0129 trial, a randomized phase III trial evaluating cisplatin-RT with conventional vs accelerated fractionation that was negative for its primary endpoint. In a recursive partitioning analysis, the authors found that the major factor for OS among patients with OPSCC was HPV status, followed by number of pack years of tobacco smoking less than or equal to 10 versus greater than 10, and, lastly, nodal stage. Patients with OPSCC were classified into 3 categories with respect to risk of death: (1) low risk: patients with HPV-positive tumors and less than N2b nodal disease; (2) intermediate risk: patients with HPV-positive tumors, greater than 10 pack-years of tobacco exposure, and nodal stage greater than or equal to N2b OR patients with HPV-negative tumors, less than or equal to 10 pack-years, and T2-T3 tumors; (3) high risk: patients with HPV-negative tumors and either T4 tumors OR greater than 10 pack-years. O'Sullivan and colleagues²³ conducted a study to identify a group of HPV-positive patients with a low risk of distant metastases that may be suitable for treatment deintensification. The investigators found that patients with HPV-associated OPSCC at low risk for distant metastatic disease (T1-T3, N0-N2a) could be treated with RT alone and recommended a clinical trial for further investigation.

Whether treatment can be deintensified in HPV-associated OPSCC is the focus of the phase III RTOG 1016 trial, for which results await. The overall goal of this study is to determine the suitability of bio-RT, that is, cetuximab-RT, as an alternative to cisplatin-RT in patients with HPV-associated OPSCC. Patients are randomized to cetuximab-RT versus cisplatin-RT. The primary objective of the trial is to evaluate whether cetuximab-RT is noninferior to cisplatin-RT, indicating that they are equivalent treatments.

ECOG 1308 tested a novel deintensification strategy for patients with HPV-positive OPSCC. Patients received induction chemotherapy and those that had a clinical complete response were eligible for a lower dose of RT.²⁴ This trial enrolled 90 patients with stages III-IVb HPV-associated OPSCC who received induction chemotherapy with paclitaxel, cisplatin, and cetuximab; 62 had a complete clinical response to chemotherapy and, therefore, went on to receive low dose intensity-modulated RT at 54 Gy with weekly cetuximab. The other 28 patients with a partial response or stable disease received the standard dose of IMRT at 70 Gy with weekly cetuximab. At 2 years, the PFS rate among patients receiving low-dose intensity-modulated RT was 80% and OS was 93%, whereas for smokers with more than a 10 pack-year history, PFS was 57% and OS was 86%. The subgroups that did well with low-dose intensity-modulated RT were smokers with fewer than 10 pack-years and non- T4, non- N2c disease, with a 2-year PFS and OS rates of 96%. Therefore, results from this study revealed that patients with T4 tumors, N2c disease and smokers were not appropriate for deintensification.

An alternative deintensification approach in HPV-associated OPSCC is the omission of chemotherapy. NRG HN-002 is a randomized phase II trial that enrolled approximately 300 patients, comparing RT alone versus cisplatin-RT in patients with HPV-positive, T1-T3 tumors, N0- N2b disease and less than or equal to 10 pack-years. Patients were randomized to receive accelerated RT alone to 60 Gy given 6 fractions a week over 5 weeks versus 60 Gy using standard fractionation over 6 weeks with dose- reduced weekly cisplatin (40 mg/m² weekly, total 240 mg/m²). This trial incorporates both a chemotherapy dose

reduction as well as RT dose reduction in both treatment arms. The primary endpoint of the study is 2-year PFS. Accrual was completed in 2017 and results are actively awaited.

In contrast to ongoing clinical trials in patients with low-risk, HPV-associated OPSCC, the role of treatment intensification is being studied in patients with intermediate-risk HPV-positive and with high-risk HPV-negative disease, in whom prognosis is unfavorable. In the definitive RT setting, multiple industry trials are evaluating the addition of immunotherapy, such as anti-PD1 or PDL1 monoclonal antibodies, to standard-of-care cisplatin-RT in patients with intermediaterisk or high-risk HNSCC.

Induction Chemotherapy

As advances in multimodality treatment of HNSCC improve LRC, the potential for multiagent systemic therapy to enhance distant control, and, therefore, OS, has been postulated. Posner and colleagues²⁵ conducted a randomized phase III trial of patients with stages III-IVb HNSCC to compare induction chemotherapy with docetaxel plus cisplatin and fluorouracil (TPF) with cisplatin and fluorouracil (PF), followed by CRT; 501 patients were randomly assigned to receive either TPF or PF induction, followed by conventionally fractionated RT with weekly carboplatin therapy. Patients who received TPF had a better OS compared with PF, making TPF the standard of care if an induction strategy is selected. The practice has not been widely adopted, however, as a suboptimal CRT regimen was used with low-dose weekly carboplatin instead of cisplatin, the standard of care. The question of whether multiagent induction followed by standard cisplatin-RT would be superior to CRT was posed by subsequent studies.

The goal of the phase III DeCIDE trial was to determine whether induction before CRT further improves survival compared with CRT alone in patients with N2 or N3 disease, a group at high risk for distant metastases.²⁶ A total of 285 treatment-naïve patients with nonmetastatic N2 or N3 HNSCC were randomly assigned to CRT alone (docetaxel, fluorouracil, and hydroxyurea plus RT) versus 2 cycles of induction (docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, and fluorouracil 750 mg/m² on days 1–5) followed by the same CRT regimen. Although the study was curtailed early due to poor accrual, there was no difference in OS between the induction and CRT arms. Therefore, the conclusion from this study was that induction cannot be recommended in patients with N2 or N3 locally advanced HNSCC.

PARADIGM was a multicenter phase III study comparing sequential therapy with CRT.²⁷ A total of 145 patients with stage III or stage IV locally advanced HNSCC were randomized to receive sequential therapy (induction with TPF × 3 then CRT with either weekly carboplatin or docetaxel depending on response to induction) or standard CRT (cisplatin 100 mg/m² on days 1 and 22 of standard RT). Results of this trial showed no significant difference in OS among patients with locally advanced HNSCC treated with sequential therapy versus concurrent CRT.

The DeCIDE and PARADIGM trials are the largest studies comparing CRT versus induction chemotherapy followed by CRT. Neither study met the planned accrual target, and, therefore, both were underpowered, making the interpretation of results challenging.

Moreover, both studies included patients with HPV-associated disease, because the use of p16 for clinical risk stratification or clinical trial selection was not yet a common practice. In both studies, the control group outperformed expectation, likely due to the inclusion of low-risk patients. These studies demonstrated no improvement in OS for the use of induction chemotherapy. A lower rate of distant metastatic disease, however, was seen in a subset analysis in the DeCIDE trial, suggesting that patients who are at high risk for metastatic disease may benefit from induction. Moreover, as immunotherapy comes of age in HNSCC, the promise of multiagent induction that includes immunotherapy has revived interest in clinical trials testing modern induction strategies.

LARYNGEAL CANCER

The broad principle that has guided clinical research to optimize the treatment of laryngeal cancer is organ preservation, in which the primary endpoint for trials is laryngectomy-free survival. For early-stage T1-T2 larynx cancers, treatment with a single modality, either larynx preservation surgery or definitive RT, leads to 90% laryngectomy-free survival. For carefully selected patients with PULA larynx cancer, who demonstrate preserved laryngeal function, absence of cartilage invasion, and good performance status, CRT is the preferred organ preservation strategy.

The Department of Veterans Affairs conducted a prospective, randomized study in patients with PULA (stage III or IV) laryngeal HNSCC and compared induction chemotherapy followed by definitive RT with conventional laryngectomy and postoperative RT²⁸; 332 patients were randomly assigned to receive either 3 cycles of chemotherapy (cisplatin and fluorouracil) followed by definitive RT or surgery and adjuvant RT. Patients in whom there was no tumor response or who had locally recurrent cancers after chemotherapy and RT underwent salvage laryngectomy. There was no difference in OS between the 2 treatment arms but there was a 64% organ preservation rate in the patients who received induction chemotherapy. This study indicated that induction and definitive RT can be effective in laryngeal preservation in a high percentage of patients without compromising OS.

The RTOG 91-11 trial compared IC with PF followed by RT, concurrent CRT using bolus cisplatin, and RT alone for organ preservation in patients with stage III and stage IV laryngeal cancer.^{29,30} The results from this study revealed a superior laryngeal preservation rate in the CRT arm compared with induction PF followed by RT or RT alone. Neither concomitant CRT nor induction chemotherapy, however, followed by RT resulted in improved OS compared with RT alone.

In 2004, Bonner and colleagues¹⁵ showed that cetuximab in addition to RT in patients with PULA HNSCC significantly increased survival without increasing toxicity. A few years later, the same investigators performed an analysis of laryngectomy-free survival in the laryngeal and hypopharyngeal subpopulation from the phase III trial comparing definitive cetuximab-RT with RT alone.³¹ A higher rate of laryngeal preservation was found for cetuximab in addition to RT. Furthermore, no significant increases in RT-induced toxicity was observed. Thus, cetuximab-RT is a standard approach when organ preservation is desired in cisplatin-ineligible patients.

SYSTEMIC THERAPY FOR RECURRENT, METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA

When a patient develops recurrent or metastatic HNSCC that is not amenable to surgical salvage or reirradiation, the goals of care become palliative. Due to the anatomic location and the burden of late toxicities, patients with recurrent, metastatic HNSCC often suffer from symptoms affecting vital human functions, such as talking, eating, and breathing. In addition to the consideration of palliative systemic therapy, the multidisciplinary care team optimally includes expertise in difficult conversations, including the risks and benefits to interventions, such as placement of a tracheostomy or feeding tube and preparation for potential acute terminal events related to loss of airway or carotid exsanguination. Early involvement of a palliative care specialist is ideal.³²

First-Line Systemic Therapy

Although depending on adequate performance status and a patient's end-of-life philosophy, palliative systemic therapy can improve both OS and quality of life in patients with recurrent, metastatic HNSCC. The EXTREME study was a randomized phase III trial that compared the classical platinum doublet (carboplatinum vs cisplatin plus fluorouracil) chemotherapy with or without cetuximab in patients with recurrent, metastatic HNSCC.³³ This study demonstrated that the addition of cetuximab conferred a benefit in OS and PFS and became the standard of care for first-line therapy for patients with recurrent, metastatic, platinum-sensitive HNSCC and a good performance status.

Second-Line Systemic Therapy

Patients with recurrent, metastatic, platinum-refractory HNSCC have a particularly poor prognosis. In this setting, platinum-refractory is defined as progression within 6 months of definitive cisplatin-RT or progression during or within 6 months of first line, platinum-based chemotherapy in the first line. Until 2016, no systemic therapy had been shown to improve OS in this population, although cetuximab monotherapy was FDA approved in 2006 on the basis of 3 single-arm, phase II studies.^{34–36} In 2016, Ferris and colleagues³⁷ reported a randomized, open-label, phase III trial that enrolled 361 patients comparing the anti-PD1 monoclonal antibody, nivolumab, to single-agent, dealer's choice systemic therapy (methotrexate, docetaxel, or cetuximab). Median OS was significantly improved in the nivolumab group, at 7.5 months versus 5.1 months in the control group. Moreover, a landmark analysis of 1-year survival showed a doubling from 17% to 36%. Similar to other cancers where immune checkpoint inhibitors have shown benefit, the so-called tail of the curve, has emerged in recurrent, metastatic HNSCC, representing a subgroup of patients with prolonged survival.

Despite the exciting advances heralded by the integration of PD1 inhibitors into the treatment paradigm, the prognosis of patients with recurrent, metastatic disease remains poor. Therefore, it is crucial to enroll patients in clinical trials to investigate novel therapeutic options and to identify biomarkers that may help improve outcomes in patients with HNSCC.

SUMMARY

Systemic therapy plays an important role in both the definitive and palliative management of patients with HNSCC. The cornerstone for curative-intent management and organ-preservation strategies remains cisplatin chemotherapy, irrespective of HPV status. Deintensification strategies are sought in good-risk HPV-positive patients, with the hypothesis that intensive multimodality regimens developed during the era of HPV-negative disease may represent overtreatment. In the setting of recurrent, metastatic HNSCC, 2 anti-PD1 monoclonal antibodies have been FDA approved in the platinum-refractory setting. New insights into the biology of immune escape by HNSCC have resulted in priority clinical trials adding immunotherapy to conventional CRT in high-risk patients. Advances in palliative and supportive care also aid the multidisciplinary team in assessing risk and benefit, communicating treatment options, managing the unique symptom burden, and comforting both patients and caregivers during the HNSCC journey.

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KEY POINTS

- Definitive treatment of previously untreated locally advanced (PULA) head and neck squamous cell carcinoma (HNSCC) includes primary surgery, including minimally invasive transoral robotic surgery (TORS) or radiation therapy.
- Systemic therapy plays an adjunctive, concurrent role during definitive or adjuvant radiation therapy.
- Deintensification strategies are under investigation for patients with low-risk, human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC).
- Treatment options for laryngeal squamous cell carcinoma are reviewed.
- Treatment options for recurrent or metastatic HNSCC are reviewed.

Current systemic therapies

Table 1

	Mechanism of Action	Key Toxicities	Indications in Head and Neck Squamous Cell Carcinoma
Cisplatin	<ul style="list-style-type: none"> Inorganic molecule that undergoes intracellular hydrolysis to produce a highly reactive charged platinum complex Inhibiting DNA synthesis by the formation of DNA cross-links Denatures the double helix Covalently binds to DNA bases and disrupts DNA function 	<ul style="list-style-type: none"> Nephrotoxicity Ototoxicity Nausea/vomiting Peripheral neuropathy Increased liver enzymes Bone marrow suppression 	<ul style="list-style-type: none"> Definitive primary treatment of locally advanced HNSCC with concurrent radiation Adjuvant treatment with postoperative radiation Induction chemotherapy Metastatic/recurrent HNSCC
Cetuximab	<ul style="list-style-type: none"> Murine-human chimeric IgG1 monoclonal antibody against human EGFR Binds the extracellular domain of EGFR, which inhibits oncogenic signaling An immune mechanism, antibody-dependent, cell-mediated cytotoxicity, is also postulated. 	<ul style="list-style-type: none"> Acneiform skin rash Fatigue Diarrhea Hypomagnesemia 	<ul style="list-style-type: none"> Definitive primary treatment of locally advanced HNSCC with concurrent radiation Adjuvant treatment with postoperative radiation Metastatic/recurrent HNSCC
5-Fluorouracil	<ul style="list-style-type: none"> Antimetabolite that inhibits thymidine synthetase, thus impeding normal RNA synthesis 	<ul style="list-style-type: none"> Alopecia Bone marrow suppression Diarrhea Cardiotoxicity Hypersensitivity reaction 	<ul style="list-style-type: none"> Induction chemotherapy Metastatic/recurrent HNSCC
Docetaxel	<ul style="list-style-type: none"> Binds to microtubules which results in inhibition of DNA, RNA, and protein synthesis 	<ul style="list-style-type: none"> Fluid retention Alopecia Bone marrow suppression Stomatitis Central nervous system toxicity 	<ul style="list-style-type: none"> Induction chemotherapy Metastatic/recurrent HNSCC
Nivolumab	<ul style="list-style-type: none"> IgG4 fully human monoclonal antibody against PD-1 Negative PD-1 receptor signaling that regulates T-cell activation and 	<p>Autoimmune toxicities:</p> <ul style="list-style-type: none"> Colitis Pneumonitis Thyroiditis Hepatitis Dermatitis 	<ul style="list-style-type: none"> Metastatic/recurrent HNSCC

Indications in Head and Neck Squamous Cell Carcinoma	Key Toxicities	Mechanism of Action
	<ul style="list-style-type: none"> Hypopharyngitis 	<p>proliferation is, therefore, disrupted</p>
	<p>Autoimmune toxicities:</p> <ul style="list-style-type: none"> Colitis Pneumonitis Thyroiditis Hepatitis Dermatitis Hypopharyngitis 	<p>Pembrolizumab</p> <ul style="list-style-type: none"> IgG4 fully human monoclonal antibody against PD-1 Negative PD-1 receptor signaling that regulates T-cell activation and proliferation is, therefore, disrupted
	<ul style="list-style-type: none"> Metastatic/recurrent HNSCC 	