JAMA | Review

Head and Neck Cancer
A Review

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IMPORTANCE Head and neck cancer, which arises in the lining or mucosa of the upper aerodigestive tract, specifically the oral cavity, oropharynx, larynx, hypopharynx, and paranasal sinuses, is the seventh most common cancer worldwide. In 2024, approximately 71 110 individuals in the US were diagnosed with head and neck cancer, and it accounted for 16 110 deaths.

OBSERVATIONS Approximately 90% of head and neck cancers are squamous cell carcinomas. Worldwide, tobacco and alcohol use are the most prevalent risk factors. In the US and Europe, 60% to 70% of newly diagnosed oropharynx cancers (a subset of head and neck cancers) are caused by human papillomavirus (HPV) infection. At presentation, approximately 30% of patients with head and neck cancer have early-stage or localized disease (tumor <4 cm without regional lymph nodes involvement), 60% have locoregionally advanced disease (tumor ≥4 cm with local invasion and/or regional lymphadenopathy) and 10% have metastatic disease. Up to 10% of oropharynx squamous cell carcinomas present as squamous cell carcinomas of unknown primary. Standard treatment for localized head and neck cancer is surgery or radiotherapy, which are each associated with a 5-year overall survival rate of 70% to 90%. For locoregionally advanced head and neck cancer, multimodality treatment includes surgery followed by postoperative radiation with or without chemotherapy or concomitant chemotherapy (with cisplatin as the preferred agent), and radiation with surgery is reserved for persistent or recurrent disease. With these treatments for locoregionally advanced head and neck cancer, 5-year overall survival rates are 25% to 60% and more than 80% for HPV-associated oropharynx cancer. Choice of treatment for locoregionally advanced head and neck cancer should involve shared decision-making and consideration of effects on speech and swallow function and appearance. First-line treatment for patients with incurable locoregional recurrences or distant metastatic disease is immunotherapy with programmed death ligand-1 inhibition (ie, pembrolizumab) alone or in combination with platinum-doublet chemotherapy. With treatment, patients with incurable locoregional recurrences or distant metastatic disease have a median survival of 12 to 15 months, and 5-year survival rates are less than 20%.

CONCLUSIONS AND RELEVANCE Head and neck cancer is the seventh most common cancer worldwide. In the US and Europe, 60% to 70% of incident oropharynx cancers are associated with HPV infection. Standard treatment for localized head and neck cancer is surgery or radiotherapy. Locoregionally advanced disease is treated with surgery followed by radiation with or without chemotherapy or concurrent chemoradiation. First-line treatment for advanced disease is immunotherapy alone or with chemotherapy.

Multimedia

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JAMA. doi:10.1001/jama.2025.21733
Published online December 15, 2025.

Head and neck cancer is the seventh most common cancer worldwide.[1,2] In 2024, approximately 58 450 individuals were diagnosed with oral cavity and pharynx cancer and 12 650 were diagnosed larynx cancer in the US. These head and neck cancers accounted for 3.6% of all US cancer diagnoses and 2.6% of cancer-related deaths.[3] Sinonasal cancers account for 3% to 5% of head and neck cancers.[4]

Although many malignancies (eg, lymphoma, skin cancers, salivary gland cancers) originate in the head and neck region, the term *head and neck cancer* typically applies to tumors arising in the lining or mucosa of the upper aerodigestive tract (**Figure 1**). Approximately 90% of head and neck cancers are caused by squamous cell carcinoma.[2] Tobacco and alcohol use are the most prevalent risk factors for head and neck cancer worldwide,[5] but human papillomavirus (HPV) accounts for 60% to 70% of oropharynx squamous cell carcinomas or cancer in the US and Europe.[6-9] Primary care clinicians may help prevent development of head and neck cancers by providing HPV vaccination, treating alcohol and tobacco use disorders, and identifying premalignant lesions for excision (**Figure 2**).

This review focuses on the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment of head and neck squamous cell carcinomas (HNSCCs) of the upper aerodigestive tract including the oral cavity, oropharynx, hypopharynx, larynx, nasal cavity, and paranasal sinuses, excluding nasopharynx cancers, the latter of which are associated with the Epstein-Barr virus and have a different pathophysiology and treatment.

Methods

A PubMed search was conducted for English-language articles of randomized clinical trials, meta-analyses, systematic reviews, and observational studies of head and neck cancer published from January 1, 2010, to July 1, 2025. We reviewed the most recent National Cancer Comprehensive Network (NCCN) guidelines on Head and Neck Cancers (version 2.2024) and prioritized recent randomized clinical trials (RCTs) based on rigor of study design, sample size, and length of follow-up. Articles published before 2010 that defined standard practices were also included. Of 13 909 articles reviewed, we included 89, comprising 29 randomized clinical trials, 10 meta-analyses, 18 systematic reviews, 6 guideline recommendations, and 26 observational and cohort studies.

Discussion and Observations

Epidemiology

Non–HPV-Associated Head and Neck Cancer

The median age at diagnosis of HNSCC is 66 years,[10] with a male-to-female incidence ratio of 2:1 to 4:1.[11] Tobacco and alcohol use are the most prevalent risk factors for development of HNSCC worldwide.[12] An International Head and Neck Cancer Epidemiology Consortium analysis of 19 case-control studies published from

Figure 1. Subsites of Head and Neck Squamous Cell Carcinomas

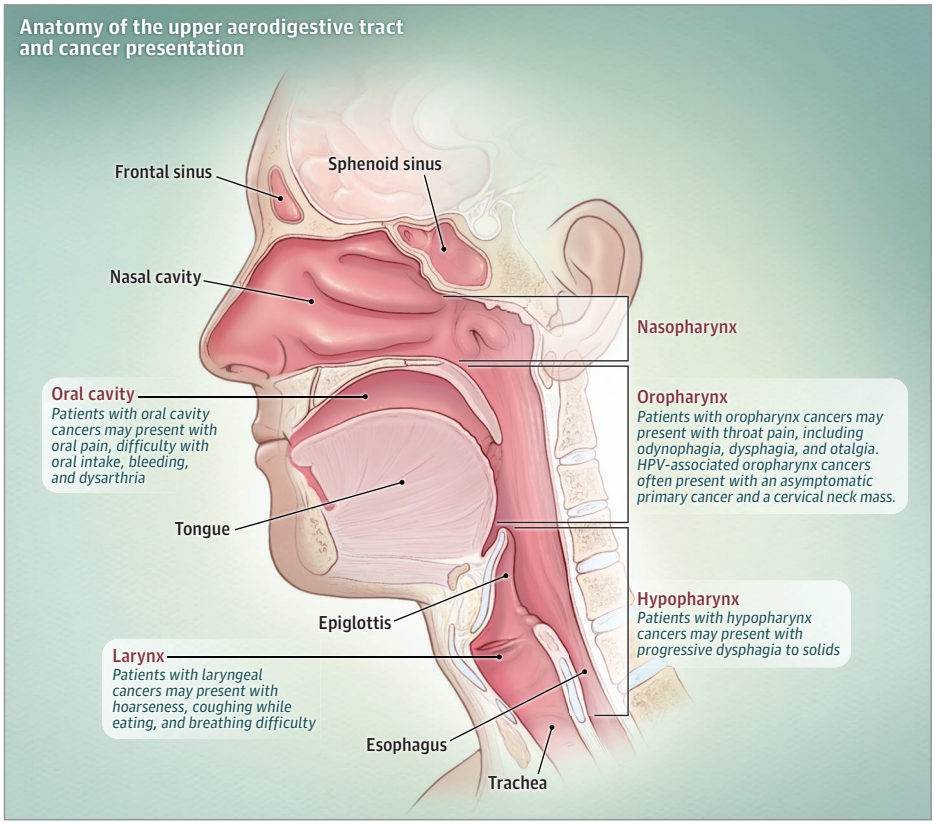
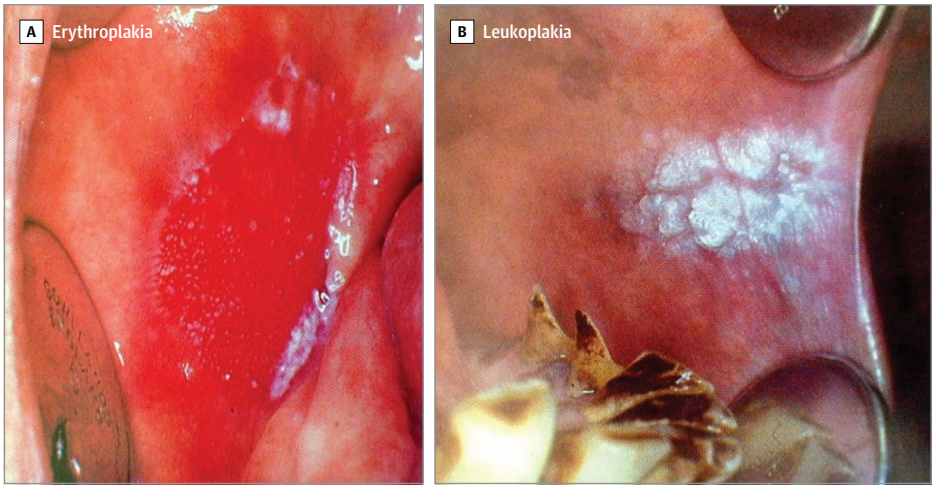


Figure 2. Precancerous Oral Cavity Lesions



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1981 to 2007 with 13 935 patients with HNSCC and 18 691 controls reported that among patients with HNSCC, 13.1% had never smoked vs 39.6% of matched controls (odds ratio, 4.52 [95% CI, 4.27-4.79]).[5] The risk of HNSCC increased progressively with each additional 10 pack-years of smoking (>50 pack-years: OR, 6.81 [95% CI, 6.24-7.44]; *P* for trend <.001).[5] HNSCC risk can be modified by smoking cessation. In a case-control study of people who formerly smoked (229 with HNSCC and 318 controls), the risk of HNSCC decreased with years of smoking cessation (compared with smoking cessation of less than 5 years duration, smoking cessation of 6-10 years: OR, 0.4 [95% CI, 0.23-0.70]; smoking cessation of >20 years: OR, 0.12 [95% CI, 0.08-0.21]).[13] Smokeless tobacco use, although less prevalent than cigarette smoking globally and in the US, is associated with an increased risk of oral cavity cancer, with a relative risk of 1.8 (95% CI, 1.1-2.9) compared with nonusers in global epidemiologic studies.[14] E-cigarettes, which first became commercially available in China in 2004 and in the US and Europe in 2007, are postulated to increase the risk of HNSCC, but have not been used long enough to produce conclusive evidence of increasing HNSCC risk.

A study of people who did not smoke cigarettes (1072 with HNSCC and 5775 controls) reported that the risk of HNSCC was higher among those who consumed 3 or more alcoholic drinks per day compared with people who did not drink alcohol (OR, 2.04 [95% CI, 1.29-3.21]; absolute data not available).[15] Another case-control study (9167 individuals with HNSCC and 12 593 controls) reported that after more than 20 years of alcohol cessation, head and neck cancer risk decreased 40% compared with the risk among people currently consuming alcohol (13% for those with >20 years cessation vs 54% for those who currently drink alcohol; OR, 0.60 [95% CI, 0.40-0.89]).[16]

Approximately 10% to 20% of people worldwide, mainly in South Asia, chew betel quid[17] (a mixture of areca nut, spices, and slaked lime [calcium hydroxide] wrapped in betel vine leaves), which is associated with increased risk of oral cavity cancer. In a study (79 cases and 149 controls), use of betel quid without tobacco use was associated with increased risk of oral cavity cancer (33% cases vs 10% controls; OR, 9.9 [95% CI, 1.76-55.62]; *P* = .009).[18]

Patients with tobacco- and alcohol-associated HNSCC often develop multiple premalignant lesions throughout the upper aerodigestive tract. In a medical record review of 3436 patients with HNSCC, 9.1% had a second primary cancer, 86% of which were squamous cell carcinomas primarily involving the head and neck (50%) or lung (34%).[19]

Patients with Fanconi anemia have germline gene variants in DNA repair genes[20] that increase the risk of developing non–HPV-associated HNSCC. Over a 20-year period, 19% of the 754 patients in the International Fanconi Anemia Registry in 2003 developed HNSCC.[20]

HPV-Associated Head and Neck Cancer

HPV is associated with 60% to 70% of new oropharynx squamous cell carcinoma diagnoses in the US and Europe (**Box 1**).[6-8] From 1988 to 2004, in the US, the incidence of HPV-positive oropharynx squamous cell carcinoma increased from 0.8 per 100 000 to 2.6 per 100 000, while incidence of HPV-negative oropharynx squamous cell carcinoma decreased from 2.0 per 100 000 to 1.0 per 100 000.[6] A study from 2013 to 2014 reported the incidence of HPV-positive oropharyngeal squamous cell carcinoma in the US was 4.62 (95% CI, 4.51-4.73) per 100 000 persons vs 1.82 (95% CI, 1.75-1.89) per 100 000 persons for HPV-negative oropharyngeal squamous cell carcinoma.[21] In a meta-analysis of 148 studies that tested 20 or more biopsies per subsite (eg, the oral cavity, oropharynx, larynx, upper aerodigestive tract), HPV 16 serotype was identified in 86.9% (95% CI, 79.2%-92.9%) of the 3946 patients with HPV-associated oropharyngeal cancer.[22] Compared with patients with HPV-negative head and neck cancer, those with HPV-positive oropharynx squamous cell carcinoma are younger (median age at diagnosis, 54 years vs 66 years), more likely to be White, have higher socioeconomic status, are more likely to not smoke, have lower levels of alcohol use, have fewer medical comorbidities, and have more sexual partners (Box 1).[6,23,24] Additionally, HPV-positive head and neck cancer develops predominantly in males. From 2005 to 2009, incidence was 8.5 per 100 000 person-years in males vs 1.8 per 100 000 person-years in females.[25]

Pathophysiology

Non–HPV-associated HNSCC is characterized by genetic alterations that disrupt normal cell cycle control and apoptosis, thereby

Box 1. Characterizations of Human Papillomavirus (HPV)–Associated Head and Neck Cancer

Subsite
Oropharynx (60%-70% are HPV-positive)

Patient Characteristics (vs Patients With HPV-Negative HNSCC)
Younger (median age at diagnosis, 54 y), no or minimal tobacco/alcohol exposure, White race, higher socioeconomic status, fewer medical comorbidities, and exposure to multiple sexual partners

Presentation
Painless neck mass or cervical lymphadenopathy with an asymptomatic, small primary tumor

Histopathologic Appearance
Immature, basaloid, and nonkeratinizing

Diagnostic Evaluation
Complete head and neck examination; nasopharyngolaryngoscopy as indicated

Biopsy of primary site or fine-needle aspiration of a neck lymph node

Evaluation of HPV p16 per immunohistochemistry
- Sensitivity: 96.8%
- Specificity: 83.3%
- Positive predictive value: 92.7%,
- Negative predictive value: 92.5%

HPV E6/E7 mRNA in-situ hybridization
- Sensitivity: 88.0%
- Specificity: 94.7%
- Positive predictive value: 97.2%,
- Negative predictive value: 79.9%

HPV E6/E7 mRNA polymerase chain reaction testing (criterion standard)

Computed tomographic (CT) imaging with contrast and/or magnetic resonance imaging with and without contrast of primary and neck

If clinically indicated, positron emission tomography/CT or chest CT

Prognosis
Favorable relative to HPV-negative head and neck squamous cell carcinomas; 80% 5-y survival

promoting uncontrolled cell proliferation. HPV-associated HNSCC involves viral oncoproteins (E6 and E7) that disrupt regulatory pathways involved in cell cycle arrest in response to DNA damage or facilitate uncontrolled cell division. E6 promotes degradation of p53, a tumor suppressor protein that normally halts cell cycle progression after DNA damage.[9]

E7 inactivates a tumor suppressor protein that regulates cell cycle progression. HPV-infected cells can then bypass cell cycle checkpoints and undergo uncontrolled cell division.

Clinical Presentation

Precursor Lesions

Twenty percent of oral cancers develop from precancerous lesions, leukoplakia, and erythroplakia, which are associated with alcohol and tobacco use (Figure 2).[26] Leukoplakia, which requires biopsy for definitive diagnosis,[27] presents as raised white plaques and has a mean malignant transformation rate of 3.5% (range, 0.13%-34.0%) with variable follow-up across 24 studies.[28] Risk factors for malignant transformation of these precancerous lesions include female sex, area of leukoplakia exceeding 200 mm^2, epithelial dysplasia on pathology, and nonhomogeneous type (red and white lesions). Erythroplakia, superficial velvety-red oral mucosal lesions,[27,29] should be biopsied or excised because 75% to 90% are carcinoma, carcinoma in-situ, or severe dysplasia and 26% progress into cancer.[29] In contrast, HPV-positive oropharynx cancers often have no precursor lesions and there are no US Food and Drug Administration (FDA)–approved screening tests for HPV-positive oropharynx cancer. HPV vaccination, which was FDA approved for females aged 9 to 26 years in 2006 and for males in 2009, will likely decrease the incidence of HPV-associated oropharynx squamous cell carcinoma, particularly in individuals without prior exposure to HPV.

Squamous Cell Carcinomas of Unknown Primary

The incidence of lymph node squamous cell carcinoma metastases without evidence of a head and neck primary tumor on examination or imaging (ie, squamous cell carcinomas of unknown primary) increased between 2000 and 2015 with rising incidence of HPV-positive oropharynx squamous cell carcinoma.[30] Up to 10% of oropharynx squamous cell carcinomas initially present as squamous cell carcinomas of unknown primary and have no primary lesion identified on physical examination and flexible nasopharynoscopy.[31] A retrospective study of 236 patients with squamous cell carcinomas of unknown primary reported that of the 53% of cases with an occult primary tumor identified by biopsy, 88% were in the oropharynx.[32]

Clinical Presentation

Presenting symptoms of HNSCC depend on the primary tumor site. Patients with oral cavity cancers may have oral pain, difficulty with oral intake, bleeding, and dysarthria. Pharyngeal cancers may present with odynophagia, otalgia, and dysphagia; laryngeal cancer with hoarseness, coughing while eating, and breathing difficulty; and hypopharynx cancer with progressive dysphagia to solids. The presenting sign of HPV-associated oropharynx squamous cell carcinoma is often an asymptomatic primary or oropharynx tumor and a cervical neck mass (51% of patients among 77 with newly diagnosed HPV-associated oropharynx cancer) (**Box 2**).[30]

Assessment and Diagnosis

Patients with oral mucosal ulcers or lesions[33] that do not resolve within several weeks, submucosal masses, bleeding, and/or localizing symptoms described above should undergo examination of the oral cavity and nasopharyngolaryngoscopy by an oral surgeon or otolaryngologist.[2]

Pathologic diagnosis of head and neck cancer can be made with a biopsy or fine-needle aspiration of a primary tumor or suspicious lymph node.[34] For diagnosis and prognostication, biopsy specimens should undergo immunohistochemistry for p16 (a protein induced by HPV viral oncogene 7) and HPV testing via HPV DNA and/or HPV RNA polymerase chain reaction testing or in-situ hybridization. Although immunohistochemistry detection of protein p16 is often used as a surrogate for HPV infection in tumors,[35] 9% of oropharynx squamous cell carcinomas positive for p16 by immunohistochemistry do not have detectable HPV DNA or mRNA.[36] For patients with squamous cell carcinomas of unknown primary, head and neck examination performed under anesthesia improves visualization of the oropharynx and facilitates tissue sampling for primary

Box 2. Commonly Asked Questions

What are the typical presentation and characteristics of patients with human papillomavirus (HPV)–associated oropharynx squamous cell carcinoma?

The presenting sign of HPV-associated oropharynx squamous cell carcinoma is often an asymptomatic cervical neck mass. Patients with HPV-associated oropharynx squamous cell carcinoma often are younger, less like to smoke or consume alcohol, have fewer medical comorbidities, more sexual partners, higher socioeconomic status and are more likely to be White than patients with HPV-negative head and neck cancer.

Are there methods to screen for or prevent HPV-positive oropharynx cancer?

There is no validated screening method for detection of HPV-positive oropharynx cancer. HPV vaccinations, typically given between the age of 9 to 26 years, will likely decrease the incidence of HPV-associated oropharynx squamous cell carcinoma, particularly in individuals without prior exposure to HPV.

When is immunotherapy recommended for treatment of head and neck cancer?

Immunotherapy is not currently recommended for treatment of early-stage and locoregionally advanced head and neck squamous cell carcinomas (HNSCC); however, checkpoint blockade with programmed cell death protein 1 inhibitors pembrolizumab and nivolumab is approved by the US Food and Drug Administration for treatment of recurrent and metastatic HNSCC.

tumor identification. HPV and Epstein-Barr virus polymerase chain reaction testing should be performed on biopsy specimens. A diagnosis of HNSCC in an adolescent or young adult without risk factors warrants an evaluation of Fanconi anemia.[20]

Imaging

Patients being evaluated for HNSCC should undergo a contrast and high-resolution computed tomography (CT) and/or magnetic resonance imaging with or without contrast of the head and neck for initial diagnosis and staging.[12] For detection of neck lymph node metastases, high-resolution CT has a sensitivity of 82% and specificity 85% and positron emission tomography (PET)/CT has a sensitivity of 90% and specificity of 94%.[37] Dedicated brain imaging is unnecessary unless patients have neurologic symptoms concerning for metastases such as headaches, cognitive changes, seizures, focal weakness, or speech difficulties.

Staging

The American Joint Committee on Cancer (AJCC) stages HNSCC uses the TMN (tumor, node, metastasis) system (8th edition staging manual) incorporating depth of invasion and extracapsular spread to identify cancers with poorer prognoses. The favorable prognoses for HPV-positive oropharynx squamous cell carcinoma is recognized with a distinct staging system.[38,39] Early-stage HNSCC (stages I and II) is localized disease with a primary tumor less than 4 cm without regional lymph node involvement; locally advanced stages (stages III and IV) involve a larger primary tumor (≥4 cm), invasion of surrounding structures, and/or regional lymphadenopathy. Approximately 90% of all patients with HNSCC are diagnosed with early-stage or locally advanced disease, which can be treated with curative intent. Advanced disease with distant metastases is a subset of stage IV disease (stage IVC).

Treatment

Management is guided by disease stage (**Table 1**).[40-43] Optimal treatment of HNSCC involves a multidisciplinary team, comprising clinicians with expertise in oncology, head and neck surgery, and radiation oncology. Patients also benefit from evaluation and treatment by dentists, speech and swallowing therapists, audiologists, dieticians, and physical and occupational therapists. Selection of treatment modality requires shared decision-making and consideration of the adverse functional and cosmetic consequences of therapy, such as dysphagia and dysarthria.[12]

Localized Disease

Standard treatment for patients with early-stage HNSCC is surgery or radiation therapy, which have similar survival outcomes (overall survival of 70%-90% at 5 years) for most early-stage HNSCC.[12] However, surgery is preferred over radiation for oral cavity and paranasal sinus cancer because radiation may cause severe adverse effects such as osteoradionecrosis (bone death due to radiation occurs in approximately 8.3% [227 of 2735] patients with head and neck cancer treated with radiation).[2,44] In contrast, for cancers of the oropharynx, larynx, and hypopharynx, radiation instead of surgery is generally recommended by some guidelines to minimize adverse effects on swallowing, speech, and voice quality.[7]

Intensity-modulated radiation therapy, which adapts the intensity of the radiation beam to the contours of the tumor to minimize effects on surrounding noncancerous tissue, is the most frequently used radiotherapy technique for treatment of head and neck cancers.[45] A trial of 94 patients with histologically confirmed pharyngeal squamous cell carcinoma (T1-4, N0-3, M0) reported decreased xerostomia among patients randomized to undergo parotid-sparing intensity-modulated radiation therapy vs conventional radiotherapy (29% [95% CI, 14%-48%] vs 83% [95% CI, 63%-95%]; $P < .001$).[46] Transoral robotic surgery is a minimally invasive surgical approach used to treat some oropharynx cancers.[47]

Prophylactic neck lymph node dissection decreases recurrence in patients with oral cavity cancer without involved lymph nodes. An RCT of 596 patients with early-stage oral cavity HPV-negative squamous cell carcinomas reported improved overall survival (80% vs 67%; $P = .01$) and disease-free survival (69.5% vs 45.9%; $P < .001$) at 3-year follow-up in patients who underwent lymph node resection compared with therapeutic node dissection at relapse.[48]

Locally Advanced Disease

For patients with locoregionally advanced HNSCC, curative intent treatment options include surgical or nonsurgical approaches.[12]

Surgery | Surgical options include resection of the primary tumor and neck or cervical lymph node dissection and postoperative radiation with or without concurrent chemotherapy. For patients with locoregionally advanced oral cavity cancers, initial treatment with surgery is preferred over radiotherapy and concurrent chemotherapy due to increased risks of developing exposed bone (maxilla or mandible), pathologic fracture, and osteoradionecrosis with high-dose radiotherapy.[49] Based on National Cancer Database data, among

Table 1. Overview of Management and Prognosis by Stage

Disease extent	Localized	Locoregionally advanced	Recurrent/metastatic
Prevalence at presentation	30%	50%-60%	10%-20%
Clinical stage per AJCC	I-II	III-IV, M0	Locoregional recurrence or M1
Treatment intent	Curative	Curative	Curative if M0 and amenable to salvage surgery and/or radiation, otherwise palliative; palliative if M1[a]
Management	Surgery (with or without postoperative radiotherapy) or radiotherapy (with surgery for persistent disease)	Surgery followed by postoperative radiation (with or without concurrent chemotherapy) or chemoradiation with surgery reserved for salvage[b]	Salvage surgery and/or radiation for locoregional recurrences, M0 if amenable; palliative radiation for oligometastatic disease and otherwise systemic therapy
5-y survival[c]	70%-90%	25%-60%; 80% for HPV-positive oropharynx cancer	20%

Abbreviation: AJCC, American Joint Committee on Cancer.

[a] M0 indicates absence of distant, metastatic disease; M1 indicates presence of distant, metastatic disease.

[b] Concurrent radiosensitizing therapy is warranted with postoperative radiation for high-risk features of microscopically positive margins and/or extranodal extension on surgical pathology.

[c] Impacted by subsite, specific stage, and human papillomavirus (HPV) status.

patients with larynx cancer and thyroid cartilage invasion, total laryngectomy (n = 353) was associated with improved survival compared with chemoradiation (n = 616) (median overall survival duration: 61 vs 39 months; $P < .001$).[50,51]

Chemoradiation | Nonsurgical treatment for locoregionally advanced HNSCC is curative intent radiation (70 Gy in 35 fractions) plus concurrent chemotherapy. Cisplatin enhances the effects of radiation (radiosensitizing) when given concurrently with radiation for curative treatment of locally advanced head and neck cancer. Guidelines recommend high-dose (100 mg/m^2) cisplatin every 3 weeks.[52,53] A meta-analysis of 107 RCTs (19 805 patients with locally advanced HNSCC) reported that concurrent surgery/radiation and chemotherapy (mostly cisplatin) improved survival, with absolute survival benefit of 6.5% and 3.6% at 5 and 10 years, respectively, compared with surgery/radiation alone or chemotherapy given before or after surgery/radiation.[54,55] In contrast, chemotherapy given before (neoadjuvant) or after surgery/radiation (adjuvant) did not improve survival.[55] For patients with contraindications to cisplatin (eg, kidney insufficiency, peripheral neuropathy, hearing impairment), an alternative chemotherapy (ie, carboplatin combination chemotherapy) may be considered. In an RCT of 226 patients with stage III or IV oropharynx carcinoma, receiving carboplatin plus fluorouracil concurrently with radiation improved 5-year overall survival vs radiation alone (22% vs 16%; $P = .05$).[56]

The decision to perform a surgical neck lymph node dissection is typically made based on a PET/CT obtained at least 12 weeks after chemoradiation. In an RCT of 564 patients with stage N2 or N3 HNSCC, those whose lymph node dissections were guided by PET/CT rather than electively planned automatically underwent fewer surgical procedures but had similar survival rates (2-year overall survival: 84.9% vs 81.5% [upper boundary of 95% CI for hazard ratio <1.50]; $P = .004$).[57]

Cetuximab | Cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor, was FDA approved in 2006 as a radiosensitizing agent based on a randomized phase 3 trial of 424 patients with locoregionally advanced HNSCC, which reported an overall survival benefit with use of cetuximab compared with radiation alone (median overall survival, 49.0 vs 29.3 months; $P = .03$).[58] However, 3 RCTs (n = 1372) of patients with HPV-associated oropharyngeal cancer (n = 1372) reported inferiority of cetuximab and radiotherapy compared with high-dose cisplatin and radiotherapy.[59-61] Additionally, an RCT that was prematurely terminated after randomization of 298 patients with locoregionally advanced HPV-positive oropharyngeal carcinoma reported lower 3-year overall survival with cetuximab and radiotherapy compared with cisplatin and radiotherapy (78% [95% CI, 71%-85%] vs 88% [95% CI, 83%-94%]; adjusted hazard ratio [HR], 1.62 [95% CI, 0.93-2.86]).[62] Incidence of locoregional failure at 3 years was also higher with cetuximab (23% [95% CI, 16%-31%]) vs cisplatin (9% [95% CI, 4%-14%]; Gray test $P = .04$).[62] Therefore, cetuximab is only advised for patients with locoregionally advanced HNSCC in whom cisplatin is contraindicated.

Postoperative Radiation

NCCN guidelines recommend addition of cisplatin to postoperative radiotherapy for patients with positive surgical margins and/or extranodal extension.[12] A pooled analysis of 2 RCTs with 793 patients with stage II-IV, M0 disease HNSCC with positive surgical margins and/or extranodal extension, reported improvement in progression-free survival (plus locoregional control, disease-free survival, and overall survival) with cisplatin plus radiation vs radiation alone (10-year disease-free survival, 18.4% vs 12.3%; $P = .05$).[63,64]

Induction Chemotherapy and Immunotherapy

Three phase 3 RTCs, including a total of 869 patients with locoregionally advanced HNSCC, showed no survival advantage with induction chemotherapy prior to concurrent chemoradiotherapy vs concurrent chemoradiotherapy alone.[65-67] However, induction chemotherapy causes rapid tumor regression, so may be useful for patients with life-threatening tumor-related complications such as airway obstruction. Phase 3 trials have established docetaxel, cisplatin, and fluorouracil as the standard induction regimen.[68-70]

Induction immunotherapy with the checkpoint inhibitor pembrolizumab has been shown to improve event-free survival among patients with locally advanced HNSCC treated with surgery. A 2025 phase 3 study randomized 363 patients with locally advanced HNSCC to undergo 2 cycles of neoadjuvant pembrolizumab and 15 cycles of adjuvant pembrolizumab in addition to standard care (surgery, adjuvant radiotherapy with or without concomitant cisplatin, depending on surgical margins) vs standard care alone (control).[71] Pembrolizumab improved event-free survival at 36 months (57.6% vs 46.4%; HR, 0.73 [95% CI, 0.58-0.92]; 2-sided $P = .008$).[71]

Table 2. Select Systemic Therapies and Associated Therapeutic Trials for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

Regimen	Trial	No. randomized	Comparator regimen	Efficacy	Common adverse events (% of patients)
First-line systemic therapy					
Pembrolizumab plus chemotherapy (cisplatin or carboplatin plus fluorouracil)[72]	KEYNOTE-048, 2019	552	Cisplatin or carboplatin, fluorouracil, and cetuximab	Total population: mOS, 13.0 vs 10.7 mo (P = .003); mPFS, 4.9 vs 5.1 mo (P = .17); ORR, 36% vs 36% CPS ≥1 population (86%): mOS, 13.6 vs 10.4 mo (P < .001); mPFS, 5.0 vs 5.0 mo (statistical analysis not performed); ORR, 36% vs 36% CPS ≥20 population (45%): 14.7 vs 11.0 mo (P < .001); mPFS, 5.8 vs 5.2 mo (P = .02); ORR, 43% vs 38%	Anemia (58%), nausea (51%), constipation (37%), neutropenia (34%), fatigue (34%), vomiting (33%), mucosal inflammation (31%), decreased appetite (29%), diarrhea (28%), stomatitis (27%)
Pembrolizumab[72] (for tumors that express PD-L1)	KEYNOTE-048, 2019	601	Cisplatin or carboplatin, fluorouracil, and cetuximab	CPS ≥1 population (85%): mOS, 12.3 vs 10.3 mo (P = .009); mPFS, 3.2 vs 5.0 mo (statistical analysis not performed); ORR, 19% vs 35% CPS ≥20 population (44%): mOS 14.8 vs 10.7 mo, P = .0007; mPFS 3.4 vs 5.0 mo, P = .4562; ORR 23% vs 36%	Fatigue (28%), hypothyroidism (18%), constipation (20%), anemia (21%), nausea (16%), diarrhea (15%), decreased appetite (15%)
Cisplatin or carboplatin, fluorouracil, cetuximab[73]	EXTREME, 2008	442	Platinum-Fluorouracil alone	mOS, 10.1 vs 7.4 mo (P = .04); mPFS, 5.6 vs 3.3 mo (P < .001); ORR, 36% vs 20% (P < .001)	Nausea (51%), anemia (47%), hypomagnesemia (40%), fatigue (36%) diarrhea (34%), constipation (33%), neutropenia (33%), mucosal inflammation (28%), decreased appetite (30%), dermatitis acneiform (29%), vomiting (28%), stomatitis (28%)[72]
Docetaxel, cisplatin, cetuximab[74]	TPExtreme, 2021	541	Cisplatin or carboplatin, fluorouracil, and cetuximab	mOS, 14.5 vs 13.4 mo (P = .23); mPFS, 6.0 vs 6.2 mo (P = .14); ORR, 57% vs 59% (P = .64)	Anemia (78%), fatigue (68%), acneiform rash (64%), hypomagnesemia (59%), nausea (51%), oral mucositis (46%), diarrhea (44%), neutropenia (42%), thrombocytopenia (37%), vomiting (32%)
Subsequent-line systemic therapy or systemic therapy for platinum-refractory disease					
Nivolumab[75]	CheckMate 141, 2016	361	Single agent methotrexate, docetaxel, or cetuximab	mOS, 7.5 vs 5.1 mo (P = .01); 1-y OS, 36.0% vs 16.6% (P = .01); mPFS, 2.0 vs 2.3 mo (P = .32); ORR, 13.3% vs 5.8%	Fatigue (14%), nausea (8.5%), rash (7.6%)
Pembrolizumab[76] (if not used as first line)	KEYNOTE-040, 2019	498	Single agent methotrexate, docetaxel, or cetuximab	mOS, 8.4 vs 6.9 mo (P = .02); mPFS, 2.2 vs 2.3 mo; ORR, 14.6% vs 10.1% (P = .06)	Hypothyroidism (13%), fatigue (13%), diarrhea (8%), rash (8%)
Docetaxel[75,77]	2016	52	Nivolumab	mOS, 5.8 vs 7.5 mo	Anorexia (35%), asthenia (30%), anemia (26%), mucositis (17%), nausea (17%), diarrhea (17%), neutropenia (13%), neuropathy (9%)
	2009	23	NA	mOS, 6.7 mo (95% CI, 1.5-10.3); mPFS, 2.1 mo (95% CI, 1.7-2.4); ORR, 13%	
Cetuximab[75,78]	2016	13	Nivolumab	mOS, 4.1 vs 7.5 mo	Rash (49%), acne (26%), asthenia (24%), nail disorder (16%), infusion-related reactions (6%)
	2007	103	NA	mOS, 3.9 mo; ORR, 13% (95% CI, 7%-21%)	
Methotrexate[75,79]	2016	46	Nivolumab	mOS, 4.6 vs 7.5 mo	Stomatitis (43%), fatigue (32%), nausea (22%), neutropenia (19%), anemia (18%)
	2015	483	Afatinib	mOS, 6.0 vs 6.8 mo (P = .70); mPFS, 1.7 vs 2.6 mo (P = .03); ORR, 6% vs 10% (P = .10)	

Abbreviations: CPS, Combined Positive Score for PD-L1; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; ORR, objective response rate; PD-L1, programmed cell death ligand 1.

Recurrent/Metastatic Disease

Systemic therapies for patients with metastatic HNSCC are listed in Table 2.[74-79] Radiation or surgery should be considered for patients with isolated metastases and for treatment of unrelated second primary cancers.[80]

First-Line Therapy

First-line treatment (Box 2) for recurrent or metastatic HNSCC is a T-cell checkpoint inhibitor such as pembrolizumab, which enhances T-cell antitumor activity by blocking the interaction of T-cell receptor programmed cell death 1 (PD-1) with tumor cell

programmed cell death ligand 1 (PD-L1). PD-L1 expression on tumor cells is scored by using the Combined Positive Score for PD-L1 (CPS), which calculates the proportion of PD-L1 positive cells in a tumor sample, with a CPS greater than 1 considered positive. In a phase 3 trial (N = 882 patients with recurrent and/or metastatic HNSCC), pembrolizumab monotherapy improved median overall survival to 12.3 months vs 10.3 months with platinum-doublet chemotherapy and cetuximab (P = .009) in patients with CPS greater than 1 and 14.9 months vs 10.7 months (P <.001) in patients with CPS greater than 20.[72] Pembrolizumab and chemotherapy (cisplatin or carboplatin and 5-fluorouracil) improved overall survival in all patients compared with chemotherapy and cetuximab (median overall survival of 13.0 vs 10.7 months; P = .003). The most common adverse effects of pembrolizumab monotherapy were fatigue (28%), anemia (21%), and hypothyroidism (18%).[72]

Before the development of pembrolizumab, platinum and 5-fluorouracil chemotherapy with cetuximab was first-line therapy and continues to be used as an alternative first-line treatment based on a phase 3 trial of 442 patients with untreated recurrent or metastatic HNSCC.[73] In this study, all patients received platinum and 5-fluorouracil chemotherapy and 222 were randomized to receive the addition of cetuximab (maximum of 6 cycles). Patients treated with cetuximab had improved overall survival compared with those treated with platinum and 5-fluorouracil chemotherapy (median overall survival of 10.1 vs 7.4 months; HR for death, 0.80 [95% CI, 0.64-0.99]).[73]

Therapy for Platinum-Refractory Disease

The checkpoint inhibitors pembrolizumab and nivolumab were FDA approved for patients with HNSCC whose cancer progressed despite platinum therapy. In a phase 3 trial of 361 patients with platinum-refractory HNSCC randomized to receive nivolumab vs a single agent (methotrexate, docetaxel, or cetuximab), the 1-year survival rate was higher in the nivolumab group compared with the standard therapy group (36.0% vs 16.6%; HR for death, 0.70 [97.7% CI, 0.51-0.96])[75] A follow-up study of these trial participants reported 24-month overall survival of 16.9% of 240 patients treated with nivolumab vs 6% of 121 patients treated with standard therapy group. Adverse effects of nivolumab were similar to those of pembrolizumab listed above.

Treatment-Associated Adverse Effects and Supportive Care

All patients with HNSCC who receive radiation to the mucosa of the upper aerodigestive track develop mucositis (severe in 62% of patients), which causes oral pain, decreased oral intake, and increased secretions.[81] Other adverse effects that may occur within 90 days of radiation-based therapy include xerostomia (20%), dermatitis (14%-20%), dysphagia (12%), neck stiffness (10%), lymphedema (7%), dysarthria, dysgeusia, weight loss, and voice changes; these symptoms may improve or resolve in the weeks or months following treatment.[56,82] Serious adverse effects occurring 90 days after initiation of radiation include trismus, stricture formation within the pharynx, hypothyroidism, and carotid artery atherosclerosis.[56] To detect and treat radiation-induced hypothyroidism, NCCN guidelines recommend checking thyroid-stimulating hormone every 6 to 12 months after completion of radiation. Platinum chemotherapy may cause nausea, ototoxicity (31%) including sensorineural hearing loss and tinnitus, sensory peripheral neuropathy, and nephrotoxicity (37%).[82] Dental problems including tooth decay and osteoradionecrosis of the jaw may affect 10% to 18% of patients with HNSCC after radiation.[83] Therefore, patients with poor dentition should receive prophylactic dental extractions prior to radiation to prevent osteoradionecrosis.

Although no evidence-based guidelines are available, systemic analgesics such as opioids, gabapentin, or topical anesthetic mouth washes such as viscous lidocaine may prevent substantial weight loss, avoid interruptions in radiation treatment, and decrease risk of hospitalization.[12] In 2 RCTs that enrolled patients with xerostomia following radiation for head and neck cancer, use of oral cholinergic agonists improved xerostomia compared with placebo (44% with pilocarpine vs 25% with placebo; P = .03 [n = 207]; 47.4% with cevimeline vs 33.3% with placebo; P = .02 [n = 570]) with the primary adverse effect of sweating.[84,85]

Speech-language therapists can improve outcomes by teaching techniques to avoid aspiration and neck range-of-motion exercises to prevent trismus and radiation fibrosis of the neck. Dieticians can advise on maintaining or enhancing caloric intake with soft or liquid diets to avoid severe weight loss and dysphagia, which may lead to feeding tube placement during HNSCC treatment. Routine prophylactic feeding tube placement in patients with HNSCC is discouraged due to potential long-term swallowing dysfunction caused by muscle atrophy from disuse.[86]

Patients with HNSCC may experience emotional distress due to pain, difficulty eating and communicating, and disfigurement after head and neck surgery.[87] Suicide rates were higher among 151 167 survivors of head and neck cancer compared with 4 219 097 patients who had 19 different types of cancer (63.4/100 000 person-years vs 23.6/100 000 person-years).[88] Suicide rates were also increased among 350 413 survivors of head and neck cancer compared with the general US population (37.9/100 000 person-years vs 11.8/100 000 person-years; standardized mortality ratio, 5.12 [95% CI, 3.83-6.41]).[40] Thus, NCCN guidelines recommend screening patients with head and neck cancer using validated questionnaires for diagnosis, treatment, and surveillance of anxiety and depression.[87]

Prognosis

HNSCC prognosis depends on the stage at presentation, site, and HPV status. Patients with early-stage (stage I-II) HNSCC have 5-year overall survival of 70% to 90%, and patients with locally advanced disease (stage III-IV) have 5-year overall survival of 25% to 60%.[2,41] Recurrences typically occur within the first 3 years after treatment completion, although late distant metastatic recurrences (>5 years from treatment completion) can occur in HPV-positive oropharynx squamous cell carcinoma.[12]

A study of 7654 patients with HPV-associated oropharynx cancer showed that patients with tumors positive for both p16 and HPV DNA had higher 5-year overall survival rates (81.1% [95% CI, 79.5%-82.7%]) compared with patients with p16-negative/HPV-positive tumors (54.7% [95% CI, 49.2%-60.9%]) and p16-positive/HPV-negative tumors (53.2% [95% CI, 46.6%-60.8%]).[36]

Compared with HPV-negative HNSCC, HPV-positive oropharynx squamous cell carcinoma has improved survival for both locally advanced disease (3-year overall survival, 82.4% vs 57.1%; P < .001)[25] and recurrent and/or metastatic disease (median overall

survival, 2.6 vs 0.8 years; 2-year overall survival, 54.6% vs 27.6%; $P < .001$).[42]

A systematic review and meta-analysis (n = 2676) reported that, compared with patients who continued to smoke, those who quit smoking at the time of head and neck cancer diagnosis or within 12 months of diagnosis had improved overall survival (HR, 0.80 [95% CI, 0.70-0.91]).[43]

Surveillance Recommendations

After completion of treatment, NCCN guidelines recommend patients undergo a complete history and physical examination by a head and neck specialist every 1 to 3 months in year 1, every 2 to 6 months in year 2, every 4 to 8 months in years 3 to 5, and every 12 months beyond 5 years.[12]

There is no evidence to support surveillance imaging in patients without evidence of persistent disease on initial posttreatment imaging performed no sooner than 12 weeks following completion of radiation-based therapy. In a 10-year retrospective study of 1114 patients without evidence of disease on posttreatment PET/CT imaging, survival did not differ among patients with recurrences detected through surveillance PET/CT and those presenting with concerning symptoms (3-year overall survival, 60% vs 54%; $P = .70$).[89]

Limitations

This review has several limitations. First, it is not a systematic review, and the quality of the included studies was not formally evaluated. Second, some relevant studies may have been missed. Third, it did not include all head and neck malignancies (such as nasopharynx cancers).

Conclusions

Head and neck cancer is the seventh most common cancer worldwide, and 90% are squamous cell carcinoma. In the US and Europe, 60% to 70% of incident oropharynx cancers are associated with HPV infection. Standard treatment for localized head and neck cancer is surgery or radiotherapy. Locoregionally advanced disease is treated with surgery followed by radiation with or without chemotherapy or concurrent chemoradiation. First-line treatment for patients with advanced disease is immunotherapy alone or with chemotherapy.

ARTICLE INFORMATION

Accepted for Publication: October 18, 2025.

Published Online: December 15, 2025. doi:10.1001/jama.2025.21733

Conflict of Interest Disclosures: Dr Dunn reported serving on an advisory board for Merck Pharmaceuticals and Regeneron Pharmaceuticals and receiving research funding from Regeneron Pharmaceuticals, Seagen, IMVAQ, Replimune, and CUE Biopharma outside the submitted work. Dr Ho reported receiving personal fees from Rgenta, Physician Education Resource, Nested, Coherus, Exelixis, Eisai, Affyimmune, NCI Steering Committee, Chinese American Hematology and Oncology Society, Northwestern, Kura Oncology, Remix Therapeutics, Endocrine Society, Merck, ExpertConnect, University of Pittsburgh, NYU Grand Rounds, Elevar Therapeutics, and Prelude Therapeutics outside the submitted work; having a patent pending for serial No. 63/193700 (Lesional Dosimetry Methods for Tailoring Targeted Radiotherapy in Cancer); and serving as a board member of the International Thyroid Oncology Group. Dr Pfister reported receiving clinical trial support from Meira Hookipa Clinical Trial Support, and Akeso; serving on an advisory board for Nykode; and serving as the chair of the Head and Neck Cancer Guidelines Panel, National Cancer Comprehensive Network, outside the submitted work.

Funding/Support: This work was supported in part by the Memorial Sloan Kettering Cancer Center support grant/core grant P30 CA008748 from the National Cancer Institute, National Institutes of Health.

Role of the Funder/Sponsor: The Memorial Sloan Kettering Cancer Center and the National Cancer Institute had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The authors appreciate the review of the manuscript and related input provided by Marc A. Cohen, MD, MPH, Sean McBride, MD, MPH, and Steven Martin, MD, from Memorial Sloan Kettering Cancer Center. No compensation was received.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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