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NCCN Guidelines® Insights
Head and Neck Cancers, Version 2.2017
Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers provide treatment recommendations for cancers of the lip, oral cavity, pharynx, larynx, ethmoid and maxillary sinuses, and salivary glands. Recommendations are also provided for occult primary of the head and neck (H&N), and separate algorithms have been developed by the panel for very advanced H&N cancers. These NCCN Guidelines Insights summarize the panel's discussion and most recent recommendations regarding the increase in human papillomavirus–associated oropharyngeal cancer and the availability of immunotherapy agents for treatment of patients with recurrent or metastatic H&N cancer.

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Please Note

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These NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their applications or use in any way.

The full and most current version of these NCCN Guidelines are available at NCCN.org.

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Release date: June 10, 2017; Expiration date: June 10, 2018

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Head and Neck Cancers
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Head and Neck Cancers

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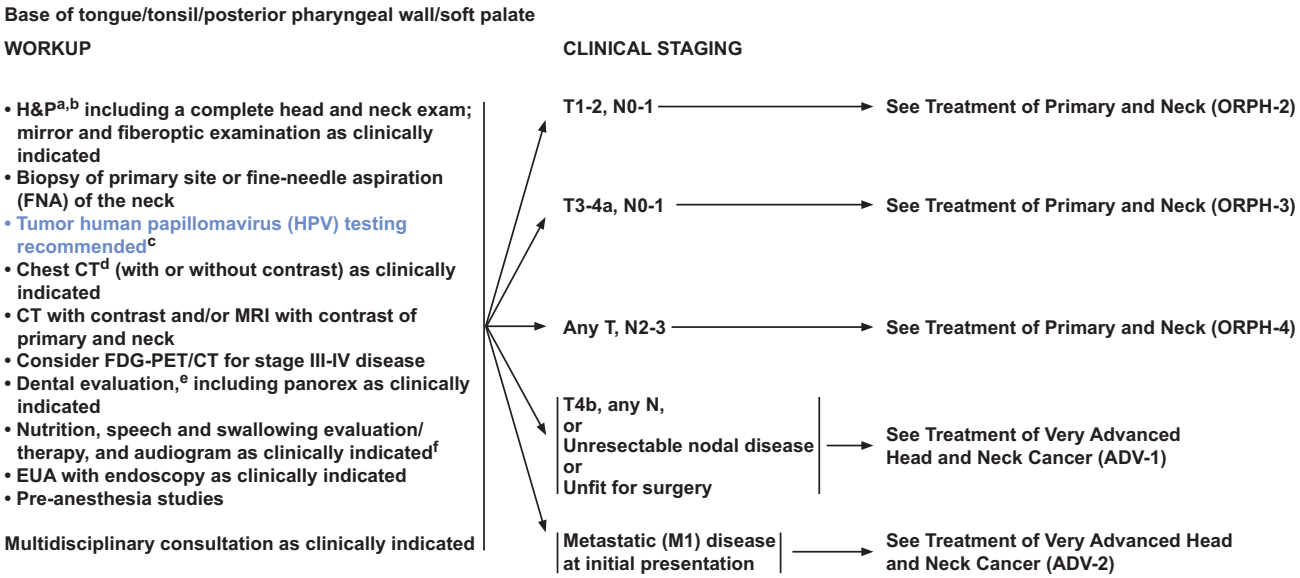
Head and Neck Cancers, Version 2.2017



[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. Smoking cessation counseling as clinically indicated. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]P16 expression is highly correlated with HPV status and is widely available. HPV in situ hybridization or PCR-based assay is also available. Although not used to guide treatment, HPV testing is valuable prognostically. The results of HPV testing should not change management decisions except in the context of a clinical trial.
[d]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.
[e]See Principles of Dental Evaluation and Management (DENT-A).
[f]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

ORPH-1

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

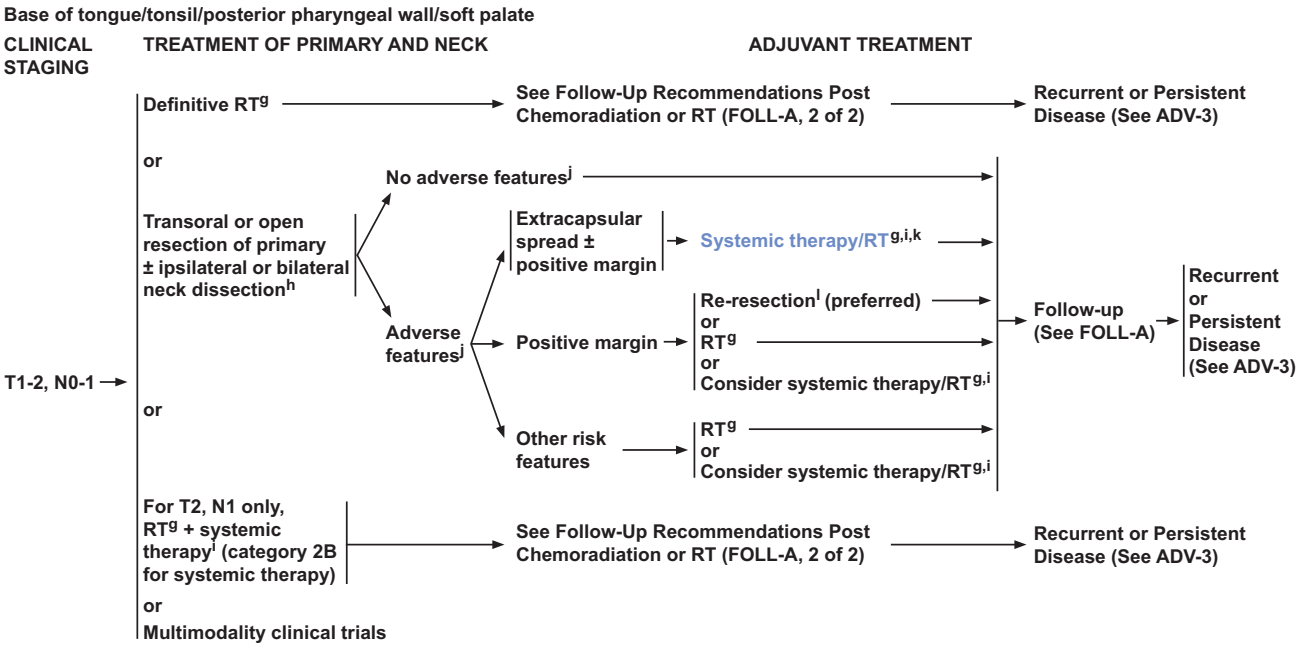
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Treatment is complex for patients with head and neck (H&N) cancers. The specific site of disease, stage, and pathologic findings guide treatment (eg, the appropriate surgical procedure, radiation targets, dose and fractionation, indications for systemic therapy). Single-modality treatment with surgery or radiation therapy (RT) is generally recommended for the approximately 30% to 40% of patients who present with early-stage disease (stage I or II). The 2 most commonly used modalities, surgery and RT, result in similar survival in these individuals. The choice of surgery or RT is often based on local institutional expertise and/or perceived relative morbidity of these treatment options. With evolving techniques of systemic therapy/RT and less invasive surgery, morbidity is also a moving target. Combined modality therapy is generally recommended for the approximately 60% of patients with locally or regionally advanced disease at diagnosis. Participation in clinical trials is a preferred or recommended



[g]See Principles of Radiation Therapy (ORPH-A).
[h]See Principles of Surgery (SURG-A).
[i]See Principles of Systemic Therapy (CHEM-A).
[j]Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).

[k]The recommendations for patients at high risk with extracapsular spread + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.
[l]Consider re-resection to achieve negative margins, if feasible.

ORPH-2

treatment option in many situations. Patients treated at high-volume centers tend to have better outcomes relative to patients treated at low-volume centers.[1,2] Revisions to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for H&N Cancers in recent years have taken into account the increase in human papillomavirus (HPV)–associated oropharyngeal cancer, as well as the recent availability of immunotherapy agents for patients with recurrent or metastatic disease.

HPV and H&N Cancer

HPV infection is associated with an estimated 4.8% of global cancers.[3] HPV is now well accepted as a cause of squamous cancers of the oropharynx (particularly cancers of the tonsils and tongue base).[4–11] The overall incidence of HPV-positive H&N cancers is increasing in the United States, whereas the incidence of HPV-negative (primarily tobacco- and alcohol-caused) cancer is decreasing.[12] Patients with HPV-associated H&N cancer tend to be younger.[11,13] The HPV-attributable fraction in newly diagnosed oropharyngeal cancer is estimated at 60% to 70% in the United States and parts of the European Union.[12,14–17] Oral HPV type 16 (HPV16) infection increases the risk of oropharyngeal cancer[4,10,18,19] and a strong causal relationship has been established[4,18]; HPV types 18, 31, and 33 are responsible for the vast majority of the remaining fraction.[11] Expression of HPV E6 and E7 oncogenes inactivates the tumor-suppressor proteins p53 and pRb, respectively, which leads to the development of cancer.[20]

Prophylactic HPV vaccination strongly decreased the incidence of cervical intraepithelial neoplasia in prospective clinical trials.[21,22] Recent data from one of these trials suggest that HPV vaccination has the potential to prevent HPV-attributed oropharyngeal cancer.[23] An unplanned analysis demonstrated a statistically significantly lower prevalence of oral HPV 16/18 infection 4 years after vaccination among HPV-vaccinated versus hepatitis A–

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PRINCIPLES OF SYSTEMIC THERAPY

- **The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).**
- **Unless otherwise specified, regimens listed below can be used for either nasopharyngeal or non-nasopharyngeal cancer.**

Recurrent, Unresectable, or Metastatic (with no surgery or RT option)

- **Combination therapy**
  - **Cisplatin or carboplatin/5-FU/cetuximab[30] (non-nasopharyngeal) (category 1)**
  - **Cisplatin or carboplatin/docetaxel[31] or paclitaxel[32]**
  - **Cisplatin/cetuximab[33] (non-nasopharyngeal)**
  - **Cisplatin/5-FU[32,34]**
  - **Cisplatin or carboplatin/docetaxel/cetuximab[35] (non-nasopharyngeal)**
  - **Cisplatin or carboplatin/paclitaxel/cetuximab[36,37] (non-nasopharyngeal)**
  - **Carboplatin/cetuximab[38] (nasopharyngeal)**
  - **Cisplatin/gemcitabine[39] (nasopharyngeal)**
  - **Gemcitabine/vinorelbine[40] (nasopharyngeal)**
- **Single agents**
  - **Cisplatin[33,41]**
  - **Carboplatin[42]**
  - **Paclitaxel[43]**
  - **Docetaxel[44,45]**
  - **5-FU[41]**
  - **Methotrexate[46,47]**
  - **Cetuximab[48] (non-nasopharyngeal)**
  - **Gemcitabine[49] (nasopharyngeal)**
  - **Capecitabine[50]**
  - **Afatinib[51] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 2B)**
  - **Pembrolizumab[52,53] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy)**
  - **Nivolumab[54] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 1)**

See References on CHEM-A 3 of 5

vaccinated women.[23] However, no formal prospective studies of the efficacy of HPV vaccines in the prevention of oral HPV infections have been conducted, and therefore further studies are warranted.

HPV Testing

The association of tumor HPV status with patient prognosis has led to clinical utility (discussed later). However, there are currently no diagnostic tests with regulatory approval. A few HPV testing options are available for use in the clinical setting. Expression of p16 as detected by immunohistochemistry (IHC) is a widely available surrogate biomarker that has very good agreement with HPV status as determined by HPV E6/E7 mRNA expression.[24–26] Other tests include HPV detection through PCR and in situ hybridization (ISH).[24,26] Sensitivity of IHC staining for p16 and PCR-based assay is high, although specificity is highest for ISH.[26] A validation study of HPV testing methods showed that the sensitivity and specificity of p16 IHC was 96.8% and 83.8%, respectively, with the sensitivity and specificity of HPV16 ISH being 88.0% and 94.7%.[24] Agreement between p16 IHC and ISH was good. The reduced specificity for p16 IHC may have been due to the presence of p16-positive tumors that do not have evidence of HPV DNA, whereas the reduced sensitivity for HPV16 ISH may been due to the presence of other high-risk HPV types in the tumor. Due to variations in sensitivity and specificity values of testing options, multiple methods may be used in combination for HPV detection.[11,26–28] Sufficient pathologic material for HPV testing can be obtained through fine-needle aspiration.[11,29]

NCCN Recommendations: For the 2016 update, the panel revised the footnote regarding HPV testing as part of the evaluation for oropharyngeal cancer to take into account that p16 IHC is widely available and highly correlated with HPV status (ORPH-1; page 763). The footnote was also revised to take into account the option of using either ISH- or PCR-based assay. Panel members note that HPV testing

may prompt questions about prognosis (ie, a favorable or a less favorable forecast) and sexual history that the clinician should be prepared to address.

HPV and Treatment of Oropharyngeal Cancer

Analyses from clinical trials indicate that patients with locally advanced HPV-positive H&N cancers experience improved response to treatment and overall survival (OS) and progression-free survival (PFS) when compared with HPV-negative tumors,[30–34] with one analysis showing that p16-positive nonoropharyngeal squamous H&N cancers have a better prognosis compared with p16-negative nonoropharyngeal cancers.[35] Treatment response is improved in patients receiving both chemoradiation[30,31] and conventional RT.[36] A systematic review including 56 prospective or retrospective studies showed that patients with p16-positive oropharyngeal cancer had a better prognosis and fewer rates of adverse events compared with those with p16-negative disease.[37] Further, patients with p16-negative disease had worse outcomes after RT relative to surgery (hazard ratio [HR], 1.66; 95% CI, 1.26–2.18; $P<.001$), and this difference was not statistically significant for patients with p16-positive disease (HR, 1.33; 95% CI, 0.94–1.87; $P=.114$).

There may also be an association between HPV status and survival in patients with recurrent or metastatic disease. Retrospective analyses from the phase III RTOG 0129 and 0522 trials[30,38] included patients with disease progression after platinum-based chemoradiotherapy (n=154) and showed that patients with p16-positive disease had greater OS relative to those with p16-negative disease (HR, 0.48; 95% CI, 0.31–0.74; $P<.001$).[33] An archival analysis from 2 ECOG trials (E1395[39] and E3301[40]), which included 129 patients with recurrent or metastatic H&N squamous cell carcinoma, showed that both HPV status (12.9 vs 6.7 months for HPV-positive vs HPV-negative; $P=.014$) and p16-positive disease (11.9 vs 6.7 months for p16-positive vs p16-negative; $P=.027$) were associated with greater median survival.[41] These studies provide substantial evidence that there is a clinically relevant prognostic difference in recurrent or metastatic disease.

Because patients with locally advanced HPV-positive oropharyngeal cancer may live longer, late toxicity and quality of life are concerns for these patients.[42,43] Therefore, consensus is increasing that HPV status should be used as a stratification factor or be addressed in separate trials (HPV-related vs -unrelated disease) for which patients with oropharyngeal cancer are eligible.[44–46] Some clinicians have recently suggested that less-intense treatment may be adequate for HPV-positive oropharyngeal cancers (ie, deintensification)[47]; however, the available data supporting this assertion are limited by retrospective analyses, variability in HPV testing method used, and short follow-up periods.[42,47–49] Deintensification treatment protocols for HPV-associated, locally advanced oropharyngeal cancer are being investigated in ongoing clinical trials. Strategies under active investigation include reducing or using response-stratified RT dose, using RT alone versus chemoradiation, using less invasive surgical procedures such as transoral robotic surgery, using sequential systemic therapy/RT, and using immunotherapy and targeted therapy agents such as cetuximab.[42,43,50] The ECOG-ACRIN phase II E1308 trial, in which patients with stage III–IV HPV16 and/or p16-positive oropharyngeal cancer (N=80) received induction chemotherapy followed by reduced-dose RT and weekly cetuximab, recently reported results showing that RT deintensification may result in equivalent or similar responses in selected patients compared with full-dose RT.[51]

The relationship between HPV and other prognostic or predictive factors such as smoking history and stage has been investigated.[52,53] For example, analyses of patients with oropharyngeal cancer who were enrolled in RTOG 9003 or 0129 (n=165) showed that smoking was associated with decreased OS and PFS, regardless of p16 status.[52] A retrospective analysis from a clinical trial showed no difference in the presence of distant metastasis in patients with p16-positive disease compared with those with p16-negative disease.[30] Additional analyses have suggested that individuals with matted nodes or N2c disease may have worse prognosis, and therefore should be excluded from deintensification trials.[47,54,55]

The panel currently recommends adjuvant systemic therapy/RT in patients with squamous cell carcinoma of the oropharynx in the presence of the adverse pathologic features of extracapsular nodal spread with (or without) positive mucosal margins. This recommendation is primarily based on results from RTOG 9501 and EORTC 22931.[56–58] However, in a review of published data from these randomized

controlled trials, it was noted that the panel's recommendations are based on studies that did not investigate the impact of HPV or p16 status.[59] However, the investigators from RTOG 9501 and EORTC 22931 point out that the prevalence of HPV-positive/p16-positive tumors was likely to be low in these trials.[60] Other limitations noted in this review included unplanned subgroup analyses, the grouping of multiple H&N subsites, inconsistent quantitative reporting, and lack of reporting on tumor and lymph node classification, treatment effect sizes, multivariable analyses, and quality-of-life outcomes. Therefore, the investigators who performed this review argued that these trials lack the generalizability necessary to rationalize the use of adjuvant systemic therapy/RT in patients with p16-positive disease.

Recent retrospective studies have not observed a statistically significant association between extracapsular spread and survival in patients with HPV-positive oropharyngeal cancer.[44,53,61–64] For example, a study of 220 patients with p16-positive oropharyngeal cancer who received surgical resection with or without adjuvant treatment showed that the presence of ≥5 metastatic nodes is associated with disease recurrence and survival, but extracapsular spread was not significantly associated with outcomes in this sample.[63] Recent studies of patients with p16-positive oropharyngeal cancer treated with surgery show that soft tissue metastasis may be associated with poor survival outcomes, especially in patients with T3–T4 disease.[53,65] These results suggest that patients with p16-positive disease with extracapsular spread could potentially be treated differently than those with p16-negative disease and extracapsular spread.

NCCN Recommendations: The panel deliberated regarding the strength and limitations of the evidence supporting the use of adjuvant systemic therapy/RT in patients with oropharyngeal cancer who have extracapsular spread. Before the 2016 update, adjuvant systemic therapy/RT for patients with extracapsular spread was a category 1 recommendation for cancer of the oropharynx, lip, oral cavity, hypopharynx, larynx, and unknown primary. For the 2016 update, the panel revised its recommendation for adjuvant systemic therapy/RT in patients with oropharyngeal cancer who have extracapsular spread from category 1 to category 2A (see ORPH-2; page 764; revisions also apply to ORPH-3 and ORPH-4). This change in category was based on a lack of high-quality, prospective clinical evidence and controversy. Adjuvant systemic therapy/RT remains a category 1 recommendation for patients with other types of H&N cancer who have extracapsular spread, including HPV-negative oropharynx cancer. Where the panel recommends adjuvant systemic therapy/RT for patients with oropharyngeal cancer and extracapsular spread, a footnote was added noting that this treatment recommendation is based on randomized studies in which HPV status was unknown, consistent with a conclusion of the review by Sinha et al.[59]

Because HPV status is a strong predictor of oropharyngeal cancer prognosis, the AJCC recently released separate staging systems for p16-positive and p16-negative oropharyngeal cancer.[66,67] However, as the panel meeting to discuss the 2017 NCCN Guidelines update was held before publication of the newest edition of the AJCC Staging Manual, the most recent version of the NCCN Guidelines for Cancer of the Oropharynx does not take into account differential staging between p16-positive and p16-negative disease. Deintensification treatment protocols for patients with HPV-related oropharyngeal cancer are currently being investigated (eg, ClinicalTrials.gov identifiers: NCT01154920, NCT01706939, NCT01302834, and NCT01855451). Panel members urge that patients with HPV-related cancers be enrolled in clinical trials evaluating biological and treatment-related questions.[42,43,68]

Immunotherapy for Recurrent and Metastatic H&N Cancer

Updates to systemic therapy recommendations made in 2016 include the addition of 2 immunotherapy agents: nivolumab and pembrolizumab (see CHEM-A 2 of 5; page 765). Nivolumab, an anti–PD-1 antibody, was assessed in a phase III randomized clinical trial including 361 patients with recurrent H&N squamous cell cancer whose disease had progressed within 6 months after platinum-based chemotherapy.[69] With a median follow-up of 5.1 months (range, 0–16.8 months), OS was significantly greater in patients randomized to receive nivolumab versus standard second-line, single-agent systemic therapy with either methotrexate, docetaxel, or cetuximab (HR, 0.70; 97.73% CI, 0.51–0.96; *P*=.01). One-year survival was also greater for patients who received nivolumab versus standard therapy (36.0%

vs 16.6%, respectively) and the response rate was higher (13.3% vs 5.8%, respectively), but median PFS was not significantly different between the groups (2.0 vs 2.3 months, respectively; *P*=.32). In prespecified exploratory analyses, the OS benefit in patients treated with nivolumab appeared to be confined to those with a tumor PD-L1 expression level of ≥1% (n=149; 8.7 vs 4.6 months; HR, 0.55; 95% CI, 0.36–0.83). In patients with tumor PD-L1 expression level <1% (n=111), no OS advantage was demonstrated for those treated with nivolumab (5.7 vs 5.8 months; HR, 0.89; 95% CI, 0.54–1.45). Grade 3 or 4 treatment-related adverse events occurred in 13.1% of patients who received nivolumab compared with 35.1% of those who received standard therapy. These results indicate that nivolumab prolongs survival in patients with recurrent or metastatic squamous cell H&N cancer that has progressed after platinum-based chemotherapy compared with those who receive standard single-agent systemic therapy.

Pembrolizumab, another anti–PD-1 antibody, was initially studied at a dose of 10 mg/kg given every 2 weeks in the squamous cell H&N cancer cohort of the KEYNOTE-012 trial.[70] Clinical activity was identified and the possibility that responses could be durable was suggested. A lower, fixed-dose schedule using pembrolizumab, 200 mg every 3 weeks was subsequently assessed in a phase Ib expansion cohort of 132 patients with recurrent or metastatic squamous cell H&N cancer[71]; 82% of these patients had previously received systemic therapy for their recurrent or metastatic disease. At 6 months, the OS rate was 59% and PFS was 23%, with an overall response rate of 18%. Observed responses appeared durable, although follow-up was limited (median, 9 months). Through scoring both tumor and immune cells, the response rate in patients who were PD-L1–positive (≥1% expression) was significantly greater than in patients who were PD-L1–negative (22% vs 4%, respectively; *P*=.021), and responses were seen in both HPV-associated and non–HPV-associated disease. Pembrolizumab was generally well tolerated, with grade 3/4 toxicities reported in only 9%, and no treatment-related deaths.[70]

Based on these studies, nivolumab and pembrolizumab received FDA approval in 2016 for use in patients with recurrent or metastatic squamous cell H&N cancer that has progressed on or after platinum-based chemotherapy. The NCCN panel recommends nivolumab for patients with this indication as a category 1 recommendation based on high-quality evidence,[69] whereas pembrolizumab is a category 2A recommendation based on results from nonrandomized trials.[70,71] Despite the ambiguities of PD-L1 testing and definitions, PD-L1 expression may be associated with better outcomes from treatment with immunotherapy for recurrent or metastatic squamous cell H&N cancer (ie, greater likelihood of response to pembrolizumab and greater survival benefit in response to nivolumab).

Summary

The incidence of HPV-positive oropharyngeal cancer is increasing in the United States, and patients with locally advanced HPV-positive H&N cancers have improved outcomes compared with those with HPV-negative tumors. However, currently there are insufficient data to recommend that patients with HPV-positive oropharyngeal cancers receive less-intense treatment relative to patients with HPV-negative cancers. HPV status is a prognostic factor, and panel members urge that patients with HPV-related cancers be enrolled in clinical trials evaluating biological and treatment-related questions. Evidence to support adjuvant systemic therapy/RT for patients with oropharyngeal cancer and extracapsular spread is based on randomized studies in which HPV status was unknown. Other recent updates to the NCCN Guidelines for H&N Cancers include the addition of the immunotherapy agents nivolumab and pembrolizumab for the treatment of patients with recurrent or metastatic H&N cancer who have progressed on or after platinum-based chemotherapy.

References

1. Wuthrick EJ, Zhang Q, Machtay M, et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. J Clin Oncol 2015;33:156–164.
2. Eskander A, Irish J, Groome PA, et al. Volume-outcome relationships for head and neck cancer surgery in a universal health care system. Laryngoscope 2014;124:2081–2088.
3. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012;13:607–615.
4. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92:709–720.

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5. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. J Natl Cancer Inst 2007;99:1801–1810.
6. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944–1956.
7. Schlecht NF, Burk RD, Adrien L, et al. Gene expression profiles in HPV-infected head and neck cancer. J Pathol 2007;213:283–293.
8. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer 2007;110:1429–1435.
9. Adelstein DJ, Ridge JA, Gillison ML, et al. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9-10, 2008, Washington, D.C. Head Neck 2009;31:1393–1422.
10. Agalliu I, Gapstur S, Chen Z, et al. Associations of oral alpha-, beta-, and gamma-human papillomavirus types with risk of incident head and neck cancer [published online ahead of print January 21, 2016]. JAMA Oncol, doi: 10.1001/jamaoncol.2015.5504.
11. Snow AN, Laudadio J. Human papillomavirus detection in head and neck squamous cell carcinomas. Adv Anat Pathol 2010;17:394–403.
12. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612–619.
13. D'Souza G, Zhang HH, D'Souza WD, et al. Moderate predictive value of demographic and behavioral characteristics for a diagnosis of HPV16-positive and HPV16-negative head and neck cancer. Oral Oncol 2010;46:100–104.
14. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294–4301.
15. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA 2012;307:693–703.
16. Nasman A, Attner P, Hammarstedt L, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int J Cancer 2009;125:362–366.
17. Mehanna H, Beech T, Nicholson T, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer—systematic review and meta-analysis of trends by time and region. Head Neck 2013;35:747–755.
18. Gillison ML, Alemany L, Snijders PJ, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine 2012;30(Suppl 5):F34–54.
19. Ndiaye C, Mena M, Alemany L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol 2014;15:1319–1331.
20. Schiffman M, Doorbar J, Wentzensen N, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Primers 2016;2:16086.
21. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915–1927.
22. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369:1861–1868.
23. Herrero R, Quint W, Hildesheim A, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One 2013;8:e68329.
24. Jordan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. Am J Surg Pathol 2012;36:945–954.
25. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus–associated oropharyngeal cancers with favorable prognosis. J Clin Oncol 2006;24:736–747.
26. Cantley RL, Gabrielli E, Montebelli F, et al. Ancillary studies in determining human papillomavirus status of squamous cell carcinoma of the oropharynx: a review. Patholog Res Int 2011;2011:138469.
27. Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. Cancer 2010;116:2166–2173.
28. Thavaraj S, Stokes A, Guerra E, et al. Evaluation of human papillomavirus testing for squamous cell carcinoma of the tonsil in clinical practice. J Clin Pathol 2011;64:308–312.
29. Begum S, Gillison ML, Nicol TL, Westra WH. Detection of human papillomavirus-16 in fine-needle aspirates to determine tumor origin in patients with metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res 2007;13:1186–1191.
30. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
31. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261–269.
32. Rischin D, Young RJ, Fisher R, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. J Clin Oncol 2010;28:4142–4148.
33. Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. J Clin Oncol 2014;32:3365–3373.
34. Posner MR, Lorch JH, Goloubeva O, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. Ann Oncol 2011;22:1071–1077.
35. Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol 2014;32:3930–3938.
36. Lassen P, Eriksen JG, Hamilton-Dutoit S, et al. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. J Clin Oncol 2009;27:1992–1998.
37. Wang MB, Liu IY, Gornbein JA, Nguyen CT. HPV-positive oropharyngeal carcinoma: a systematic review of treatment and prognosis. Otolaryngol Head Neck Surg 2015;153:758–769.
38. RTOG 0522: a randomized phase III trial of concurrent accelerated radiation and cisplatin versus concurrent accelerated radiation, cisplatin, and cetuximab [followed by surgery for selected patients] for stage III and IV head and neck carcinomas. Clin Adv Hematol Oncol 2007;5:79–81.
39. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562–3567.
40. Argiris A, Buchanan A, Brockstein B, et al. Docetaxel and irinotecan in recurrent or metastatic head and neck cancer: a phase 2 trial of the Eastern Cooperative Oncology Group. Cancer 2009;115:4504–4513.
41. Argiris A, Li S, Ghebremichael M, et al. Prognostic significance of human papillomavirus in recurrent or metastatic head and neck cancer: an analysis of Eastern Cooperative Oncology Group trials. Ann Oncol 2014;25:1410–1416.
42. Psyrri A, Rampias T, Vermorken JB. The current and future impact of human papillomavirus on treatment of squamous cell carcinoma of the head and neck. Ann Oncol 2014;25:2101–2115.
43. Mehanna H. Update on de-intensification and intensification studies in HPV. Recent Results Cancer Res 2017;206:251–256.
44. Kaczmar JM, Tan KS, Heitjan DF, et al. HPV-related oropharyngeal cancer: risk factors for treatment failure in patients managed with primary transoral robotic surgery. Head Neck 2016;38:59–65.
45. Dahlstrom KR, Garden AS, William WN Jr, et al. Proposed staging system for patients with HPV-related oropharyngeal cancer based on nasopharyngeal cancer N categories. J Clin Oncol 2016;34:1848–1854.
46. Gillison ML. Human papillomavirus and oropharyngeal cancer stage. J Clin Oncol 2016;34:1833–1835.
47. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol 2013;31:543–550.
48. Quon H, Forastiere AA. Controversies in treatment deintensification of human papillomavirus-associated oropharyngeal carcinomas: should we, how should we, and for whom? J Clin Oncol 2013;31:520–522.
49. Masterson L, Moualed D, Masood A, et al. De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cochrane Database Syst Rev 2014;2:CD010271.
50. Kofler B, Laban S, Busch CJ, et al. New treatment strategies for HPV-positive head and neck cancer. Eur Arch Otorhinolaryngol 2014;271:1861–1867.
51. Marur S, Li S, Cmelak AJ, et al. E1308: phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx- ECOG-ACRIN Cancer Research Group [published online ahead of print December 28, 2016]. J Clin Oncol, JCO2016683300.

52. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol 2012;30:2102–2111.
53. Sinha P, Lewis JS Jr, Piccirillo JF, et al. Extracapsular spread and adjuvant therapy in human papillomavirus-related, p16-positive oropharyngeal carcinoma. Cancer 2012;118:3519–3530.
54. Spector ME, Gallagher KK, Light E, et al. Matted nodes: poor prognostic marker in oropharyngeal squamous cell carcinoma independent of HPV and EGFR status. Head Neck 2012;34:1727–1733.
55. Vainshtein JM, Spector ME, Ibrahim M, et al. Matted nodes: High distant-metastasis risk and a potential indication for intensification of systemic therapy in human papillomavirus-related oropharyngeal cancer. Head Neck 2016;38(Suppl 1):E805–814.
56. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–1952.
57. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–1944.
58. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–850.
59. Sinha P, Piccirillo JF, Kallogjeri D, et al. The role of postoperative chemoradiation for oropharynx carcinoma: a critical appraisal of the published literature and National Comprehensive Cancer Network guidelines. Cancer 2015;121:1747–1754.
60. Cooper JS, Fortpied C, Gregoire V, et al. The role of postoperative chemoradiation for oropharynx carcinoma: a critical appraisal revisited. Cancer 2017;123:12–16.
61. Iyer NG, Dogan S, Palmer F, et al. Detailed analysis of clinicopathologic factors demonstrate distinct difference in outcome and prognostic factors between surgically treated HPV-positive and negative oropharyngeal cancer. Ann Surg Oncol 2015;22:4411–4421.
62. Maxwell JH, Ferris RL, Gooding W, et al. Extracapsular spread in head and neck carcinoma: impact of site and human papillomavirus status. Cancer 2013;119:3302–3308.
63. Sinha P, Kallogjeri D, Gay H, et al. High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. Oral Oncol 2015;51:514–520.
64. Geiger JL, Lazim AF, Walsh FJ, et al. Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. Oral Oncol 2014;50:311–318.
65. Sinha P, Lewis JS Jr, Kallogjeri D, et al. Soft tissue metastasis in p16-positive oropharynx carcinoma: prevalence and association with distant metastasis. Oral Oncol 2015;51:778–786.
66. Amin M, Edge S, Greene F, et al. AJCC Cancer Staging Manual, 8th ed. New York, NY: Springer; 2017.
67. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers-major changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. CA Cancer J Clin 2017;67:122–137.
68. Mehra R, Ang KK, Burtness B. Management of human papillomavirus-positive and human papillomavirus-negative head and neck cancer. Semin Radiat Oncol 2012;22:194–197.
69. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–1867.
70. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956–965.
71. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort [published online ahead of print September 19, 2016]. J Clin Oncol, pii: JCO681478.

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Posttest Questions

1. HPV testing options include the following:
   a. p16 IHC
   b. HPV16 ISH
   c. HPV testing by PCR-based assay
   d. All of the above
2. True or False: HPV-positive oropharyngeal cancers generally have a worse prognosis when compared with HPV-negative oropharyngeal cancers.
3. For a patient with metastatic squamous cell carcinoma of the oral cavity which has progressed on cisplatin, which treatment option is recommended as a category 1 option in the NCCN Guidelines for Head and Neck Cancers?
   a. Nivolumab
   b. Pembrolizumab
   c. Cisplatin/gemcitabine
   d. Vinorelbine
   e. Cetuximab + concurrent RT