NCCN: Continuing Education

Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: March 10, 2022; Expiration date: March 10, 2023

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

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients.

Individuals Who Provided Content Development and/or Authorship Assistance:

The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.
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The faculty listed below have the following relevant financial relationship(s) with ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

David Pfister, MD, Panel Chair, grant/research support from Bristol-Myers Squibb Company, Genentech, Inc., Cue Biopharma, Hookipa Pharma Inc., Kura Oncology, Inc., Merck & Co., Inc., and Novartis Pharmaceuticals Corporation; and data safety monitoring committee member for Boehringer-Ingelheim, GmbH.
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David M. Brizel, MD, Panel Member, royalty income from UpToDate.
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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Head and Neck Cancers, Version 1.2022

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Head and Neck Cancers address tumors arising in the oral cavity (including mucosal lip), pharynx, larynx, and paranasal sinuses. Occult primary cancer, salivary gland cancer, and mucosal melanoma (MM) are also addressed. The specific site of disease, stage, and pathologic findings guide treatment (eg, the appropriate surgical procedure, radiation targets, dose and fractionation of radiation, indications for systemic therapy). The NCCN Head and Neck Cancers Panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. These NCCN Guidelines Insights summarize the panel's most recent recommendations regarding management of HPV-positive oropharynx cancer and ongoing research in this area.

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[*]Provided content development and/or authorship assistance.

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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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

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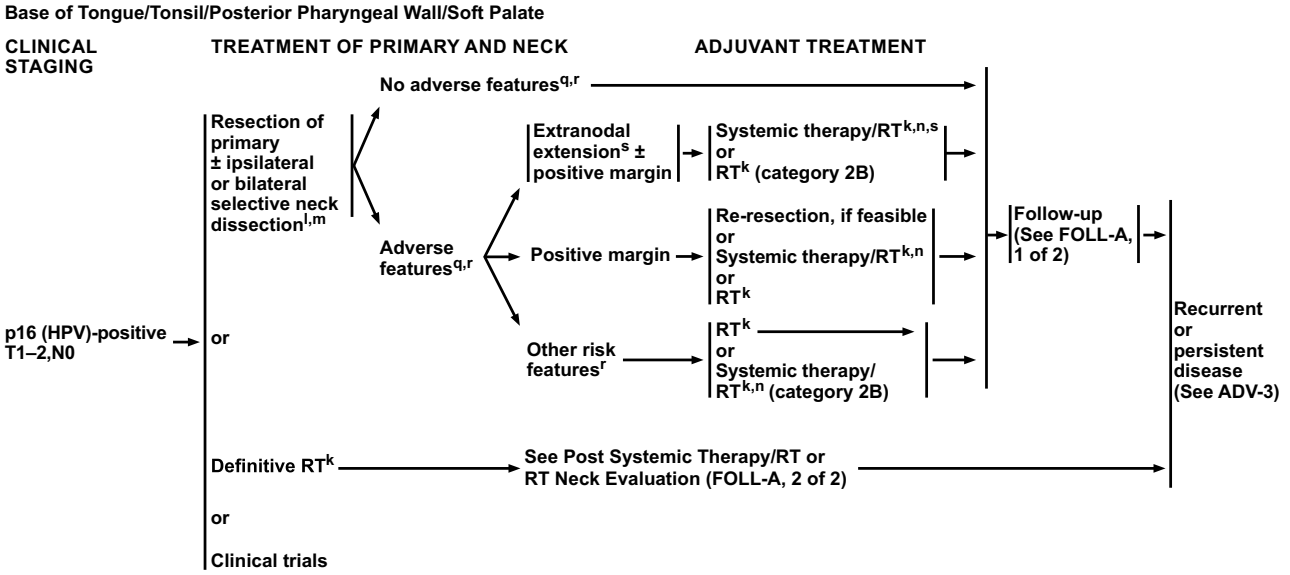

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[m] Tumors in the base of tongue, posterior pharyngeal wall, and soft palate require consideration of bilateral neck treatment as do tumors of the tonsil invading the tongue base.
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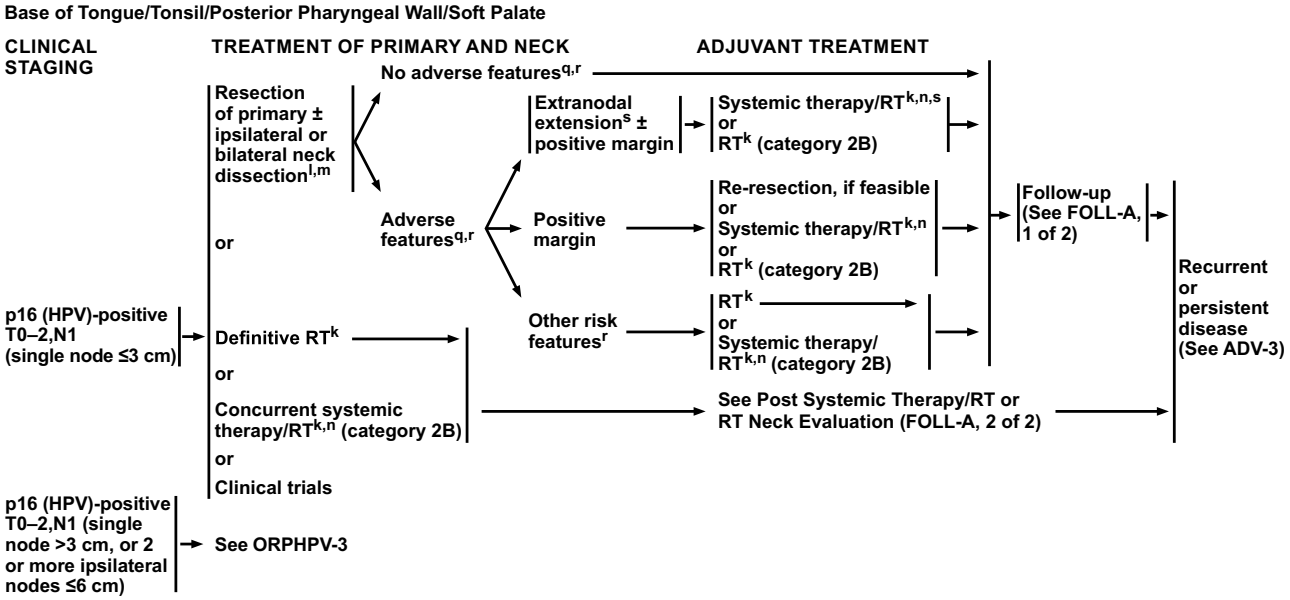
ORPHPV-1

Overview

The overall incidence of HPV-positive oropharynx cancers is increasing in the United States, whereas the incidence of HPV-negative (primarily tobacco- and alcohol-related) cancer is decreasing.[1] The attributable fraction for HPV in newly diagnosed oropharyngeal cancer is estimated to be 60% to 70% in the United States and parts of the European Union.[1–5] Patients with HPV-positive cancer have tended to be younger[6,7]; however, HPV-positive oropharynx cancer rates are increasing among older adults as the exposed cohorts age.[8,9] Oral HPV16 infection increases the risk of oropharynx cancer,[10–13] and a strong causal relationship has been established.[10,11] HPV16 accounts for approximately 90% of cases, and HPV18, 33, and 35 are responsible for the vast majority of the small remaining fraction.[6] The prevalence of HPV16 is higher in oropharyngeal cancer than in cervical cancer (~50%), in which HPV18 is also highly prevalent.[2,14–16] Expression of the HPV E6 and E7 oncogenes inactivates the tumor suppressor proteins p53 and pRb, respectively, which are frequently mutated in tobacco-related mucosal squamous cell carcinomas. Inactivation of p53 and pRb promotes genomic instability and the development of cancer, and is responsible for the upregulation of p16 protein expression, a reliable surrogate marker of the presence of HPV DNA in these tumors. Genetic profiling of HPV-positive cancer has demonstrated it to be genetically distinct from HPV-negative squamous cell carcinoma of the head and neck (SCCHN).[17]

Analyses from the National Health and Nutrition Examination Survey (2011–2014), including 2,627 adults aged 18 to 33 years, showed that HPV vaccination was associated with reduced vaccine-type oral HPV infection (0.1% in vaccinated individuals vs 1.6% in unvaccinated individuals; P=.008).[18] Moreover, HPV vaccination in the United States has led to herd protection against oral HPV16, 18, 6, and 11 infections in unvaccinated men.[19] Results of an ongoing randomized clinical trial to investigate the efficacy of HPV vaccines for the prevention of oral HPV infections have not yet been reported. Although data are not yet available, the HPV types that cause the overwhelming majority of SCCHN are included in the HPV nonavalent vaccine (provides protection against 9 high-risk HPV types). Since there is evidence that vaccination prevents HPV-related cervical and anal cancers,[20–22] the FDA expanded the indication for HPV vaccination to include prevention of oral HPV infections and related oropharyngeal cancers in 2020.



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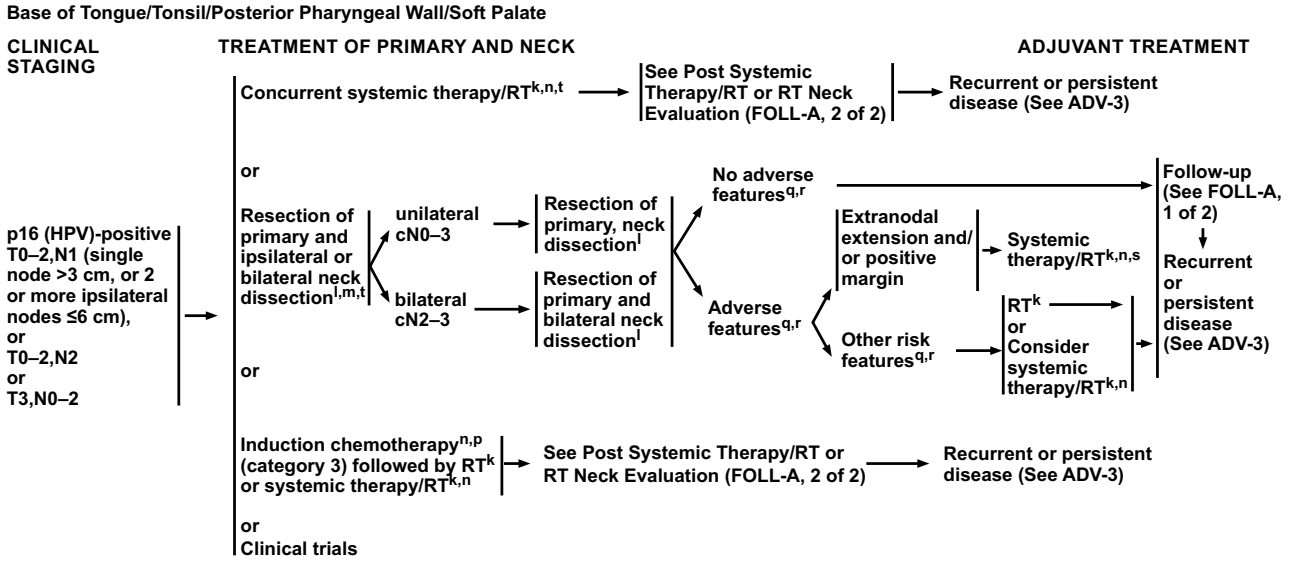
ORPHPV-2

Patients with locally advanced HPV-positive SCCHN have improved response to treatment and survival (overall survival [OS] and progression-free survival [PFS]) when compared with HPV-negative tumors.[23–29] Treatment response is improved in patients receiving radiation therapy (RT) or chemoradiation.[23,30,31] A meta-analysis including 18 studies with 4,424 patients with SCCHN showed that patients with tumors that were both HPV-positive and p16-positive had better 5-year OS and 5-year disease-free survival (DFS) than patients with tumors that were HPV-negative/p16-negative, HPV-positive/p16-negative, and HPV-negative/p16-positive.[32] However, patients with tumors that were HPV-negative/p16-positive had greater 5-year OS than patients with tumors that were p16-negative (regardless of HPV status). Discrepancies between HPV status and p16 status are usually attributable to use of assays for HPV detection that do not cover all high-risk HPV types.[33]

The impact of smoking and cancer stage on survival of patients with HPV-positive SCCHN has been investigated in numerous studies.[34–36] 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.[34] An analysis of data compiled from 4 cooperative group trials estimated that never smokers had a 51% (hazard ratio [HR], 0.40; 95% CI, 0.33–0.75) reduction in risk of cancer progression when compared with former and current smokers with HPV-positive SCCHN.[36] A retrospective analysis from a clinical trial (RTOG 0129) showed no difference in the rate of distant metastasis in patients with p16-positive versus p16-negative disease.[23] Additional analyses have suggested that individuals with T4 or N3 disease or radiographically detectable matted lymph nodes may have a worse prognosis, and therefore should be excluded from deintensification trials.[37–40] These studies on prognostic and predictive factors in HPV-positive oropharyngeal cancers form the basis for RT deintensification studies. Moreover, the striking difference in prognosis for HPV-positive versus HPV-negative SCCHN led to the creation of new AJCC staging criteria in 2018 (see later section on "Treatment," page 228).

HPV Testing

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers recommend tumor HPV testing by p16 immunohistochemistry (IHC) in all patients diagnosed with an oropharyngeal cancer. There are



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[t] For those with clinical evidence of fixed or matted nodes or obvious extranodal extension, resection is not recommended and concurrent systemic therapy/RT is preferred.

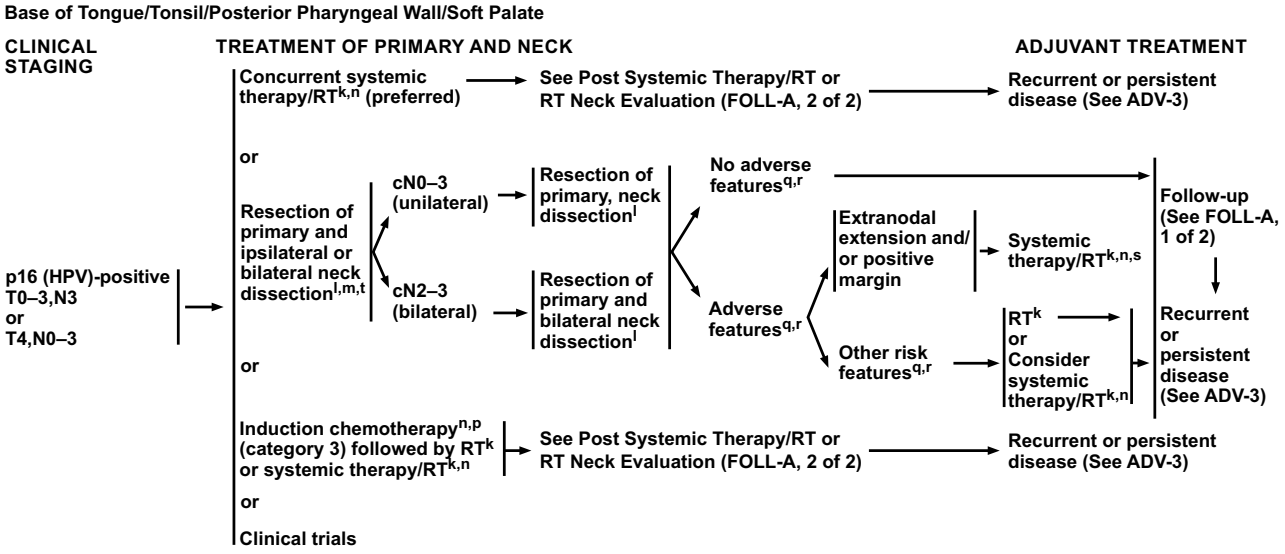
ORPHPV-3

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 IHC is a widely available surrogate biomarker that has very good agreement with HPV status as determined by HPV E6/E7 mRNA expression.[33,41–44] Other tests include HPV detection by PCR and in situ hybridization (ISH).[33,42] Sensitivity of IHC staining for p16 and PCR-based assay is high, although specificity is highest for ISH.[42] Analyses of HPV testing methods have shown that sensitivity and specificity of p16 IHC range from 94% to 97% and 83% to 84%, respectively, with sensitivity and specificity of HPV16 ISH ranging from 85% to 88% and 88% to 95%.[33,43] The reduced specificity for p16 IHC may be due to the presence of p16-positive tumors that do not have evidence of HPV DNA, whereas the reduced sensitivity for HPV16 ISH may be 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.[6,42,43,45,46] Sufficient pathologic material for HPV testing can be obtained by fine-needle aspiration.[6,47] Guidelines for HPV testing have been published by the College of American Pathologists.[48] HPV testing may prompt questions about prognosis and sexual history that the clinician should be prepared to address.

Treatment

Expert consensus is that HPV status should be used as a stratification factor in clinical trials, or clinical trial eligibility should be restricted to one or the other patient population.[49–51] With some exceptions, the treatment algorithms in the NCCN Guidelines for Head and Neck Cancers for p16-negative and p16-positive oropharyngeal cancer are identical. It is the stance of the panel that there is currently no evidence that the staging criteria published in the 8th edition of the *AJCC Cancer Staging Manual*[52] should drive clinical decision-making, as it is currently unknown how to therapeutically address the vast biologic differences between the 2 distinct cancers. The panel urges that patients with HPV-positive cancers be enrolled in clinical trials evaluating biologic and treatment-related questions.[53–55]

Some clinicians have suggested that less-intense treatment may be adequate for HPV-positive oropharyngeal cancers (ie deintensification).[38] Although not considered deintensification, other RT-based strategies that may be used to potentially minimize harm in patients with p16-positive oropharyngeal cancer include use of image-guided RT and consideration of unilateral neck irradiation in disease that is well-lateralized.[56] Available data supporting



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ORPHPV-4

these assertions are limited by retrospective analyses, single-institution phase III trials, variability in HPV testing method used, and short follow-up periods.[38,54,57,58] Deintensification treatment protocols for HPV-positive 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 laser microsurgery or transoral robotic surgery (TORS), using sequential systemic therapy/RT, and using immunotherapy.[54,56,59]

Early-stage (ie, T1–T2N0) p16-positive oropharyngeal cancers may be treated with definitive RT or resection of the primary with neck dissection[60–63] (see ORPHPV-1, page 226). Tumors at or approaching the midline (ie, tumors in the base of the tongue, posterior pharyngeal wall, soft palate, and tonsil invading the tongue base) are at risk for contralateral metastasis and warrant bilateral treatment. The randomized phase II ORATOR trial aimed to compare swallow-related QoL outcomes in patients with early-stage T1–T2,N0–2 oropharyngeal cancer treated with primary RT or systemic therapy/RT versus those treated with TORS with neck dissection with or without adjuvant RT or systemic therapy/RT.[64] The study enrolled 68 patients from 6 hospitals in Canada and Australia (88% were p16-positive), and compared MD Anderson Dysphagia Inventory (MDADI) scores between the 2 groups at 1 year. Swallow-related QoL outcomes reached statistical significance favoring the primary RT cohort; however, this difference did not meet criteria for a clinically meaningful change, and with long-term follow-up the difference in scores became less pronounced with the passage of time.[64,65] Study results showed that there were excellent and similar PFS and OS rates in both arms. The authors concluded that "RT- and TORS-based approaches were associated with clinically similar QoL outcomes, but differing spectra of toxicities, and differences in QoL between arms decreased over time. Clinicians and patients should be involved in shared decision-making, in a multidisciplinary context, to individualize treatment of oropharyngeal squamous cell carcinoma."[65] Additional randomized trials of minimally invasive transoral surgery or RT for oropharyngeal cancer are ongoing or have been presented in abstract form (ClinicalTrials.gov identifiers: NCT02984410, NCT05144100, and NCT03210103[66]).

Results from multiple phase II trials show that RT deintensification is associated with promising PFS rates in patients with p16-positive oropharyngeal cancer.[67–71] A phase II randomized trial of low-risk HPV-associated

PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:
RT Alone
- **PTV**
  - **High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]**
    - ◊ **Fractionation:**
      - **IMRT planning can consist of sequential IMRT (S-IMRT) or simultaneous integrated boost (SIB) techniques. Equivalent doses in 2 Gy (EQD2) can be used to determine appropriate fractionation schemes when using SIB techniques.**
      - **66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction);[3] daily Monday–Friday in 6–7 weeks[2]**
      - **Concomitant boost accelerated RT:**
        - **72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)**
        - **66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)**
      - **Hyperfractionation for T2,N0–1 disease: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)**
      - **69.96 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks**
  - **Low to intermediate risk: Sites of suspected subclinical spread**
    - ◊ **44–50 Gy (2.0 Gy/fraction) used for S-IMRT or the use of an anterior neck field and to 54–63 Gy (1.6–1.8 Gy/fraction) when using SIB techniques[4]**
- **Treatment de-intensification is an area of active research, with several published phase II studies demonstrating promising rates of progression-free survival with dose-reduced radiotherapy.[5]**

CONCURRENT SYSTEMIC THERAPY/RT:[6,7]
- **PTV**
  - **High risk: Typically 70 Gy (2.0 Gy/fraction)**
  - **Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4]**

Either IMRT (preferred) or 3D-CRT is recommended for cancers of the oropharynx in order to minimize dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

[1] See Principles of Radiation Techniques (RAD-A) and Discussion.
[2] For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
[3] Eisbruch A, et al. Int J Radiat Oncol Biol Phys 2010;76:1333-1338.
[4] Suggest 44–50 Gy in 3D-CRT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[5] Yom SS, et al. J Clin Oncol 2021;39:956-965; Chera BS, et al. J Clin Oncol 2019;37:2661-2669.
[6] See Principles of Systemic Therapy for Non-Nasopharyngeal Cancers (SYST-A).
[7] Based on published data, concurrent systemic therapy/RT most commonly uses conventional fractionation at 2.0 Gy per fraction to a typical dose of 70 Gy in 7 weeks with single-agent cisplatin given every 3 weeks at 100 mg/m^2; 2–3 cycles of chemotherapy are used depending on the radiation fractionation scheme (RTOG 0129) (Ang KK, et al. N Engl J Med 2010;363:24-35). When carboplatin and 5-FU are used, the recommended regimen is standard fractionation plus 3 cycles of chemotherapy. [Bourhis J, et al. Lancet Oncol 2012;13:145-153]. Other fraction sizes (eg, 1.8 Gy, conventional), multiagent chemotherapy, other dosing schedules of cisplatin, or altered fractionation with chemotherapy are efficacious, and there is no consensus on the optimal approach. In general, the use of concurrent systemic therapy/RT carries a high toxicity burden; altered fractionation or multiagent chemotherapy will likely further increase the toxicity burden. For any systemic therapy/RT approach, close attention should be paid to published reports for the specific chemotherapy agent, dose, and schedule of administration. Systemic therapy/RT should be performed by an experienced team and should include substantial supportive care. See Discussion.

oropharyngeal cancer (≤10 pack years, T1–2N1 or T3N0–1) demonstrated that de-escalated RT to 60 Gy with concurrent cisplatin was associated with a 2-year PFS rate of 90.5%, and accelerated RT alone to 60 Gy was associated with a 2-year PFS rate of 87.6%.[72] The former, but not the latter, regimen met criteria for further study and is the subject of an ongoing cooperative group phase II/III randomized trial on dose de-escalation. Similarly, a nonrandomized phase II study of definitive RT to 60 Gy ± concurrent cisplatin in 114 patients with T0–3N0–2M0 p16-positive oropharyngeal cancer demonstrated a 2-year PFS of 86% and 2-year OS of 95%.[70] Analyses of quality of life (QoL) outcomes from one of these trials[68] showed that RT deintensification was associated with a quicker and more robust return to baseline-level functioning.[73] A prospective phase II trial of initial TORS followed by risk-adapted adjuvant treatment demonstrated a 2-year PFS rate of 96.9% for low-risk disease with TORS alone, 94.9% for intermediate-risk disease with 50 Gy adjuvant RT, 96% for intermediate-risk disease with 60 Gy adjuvant RT, and 90.7% for high-risk disease with 66 Gy adjuvant RT with concurrent weekly cisplatin.[74]

Research on the impact of adverse features such as extranodal extension and number of involved nodes on outcomes in patients with p16-positive disease who have undergone resection is rapidly evolving. Analyses from the RTOG 9501[75] and EORTC 22931 trials,[76] prior to the era of p16/HPV testing, showed that extranodal extension is associated with poor prognosis and demonstrated benefit to adjuvant systemic therapy/RT in patients with locally advanced SCCHN who have undergone surgical resection.[77] Data suggesting equivalent outcomes of adjuvant RT and systemic therapy/RT for p16-positive oropharyngeal cancer with extranodal extension are restricted to retrospective trials,[35,49,78–83] although clinical trials are being conducted to validate the revised AJCC staging[52] for clinical decision-making. Secondary to a lack of high-quality, prospective clinical evidence in the modern era, systemic therapy/RT is a category 2A option for patients with p16-positive disease and extranodal extension. Adjuvant systemic therapy/RT remains a category 1 recommendation for patients with nonoropharyngeal SCCHN who have extranodal extension. Because patients with p16-positive oropharyngeal cancer have a generally favorable prognosis and may live longer, toxicity and QoL are concerns for these patients.[54,55] On the other hand, they are also younger, with fewer comorbidities, so they can probably tolerate combined adjuvant therapy better.

PRINCIPLES OF RADIATION THERAPY[1]

POSTOPERATIVE:
RT or Concurrent Systemic Therapy/RT[8-12]
- **Preferred interval between resection and postoperative RT is ≤6 weeks.**
- **PTV**
  - **High risk: Adverse features such as positive margins[13,14]**
    - **60–66 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks**
  - **Low to intermediate risk: Sites of suspected subclinical spread**
    - **44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4]**

Either IMRT (preferred) or 3D-CRT is recommended for cancers of the oropharynx in order to minimize dose to critical structures. Use of proton therapy is an area of active investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy.

[1] See Principles of Radiation Techniques (RAD-A) and Discussion.
[4] Suggest 44–50 Gy in 3D-CRT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[8] See Principles of Systemic Therapy for Non-Nasopharyngeal Cancers (SYST-A).
[9] Bernier J, et al. N Engl J Med 2004;350:1945-1952.
[10] Cooper JS, et al. N Engl J Med 2004;350:1937-1944.
[11] Bernier J, et al. Head Neck 2005;27:843-850.
[12] Cooper JS, et al. Int J Radiat Oncol Biol Phys 2012;84:1198-1205.
[13] Adverse features for p16(HPV)-negative disease: extranodal extension, positive margins, close margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular invasion, lymphatic invasion (See Discussion).
[14] Adverse features for p16 (HPV)-positive disease: extranodal extension, positive margins, close margins, pT3 or pT4 primary, one positive node >3 cm or multiple positive nodes, nodal disease in levels IV or V, perineural invasion, vascular invasion, lymphatic invasion (see Discussion). The definition of an adverse feature in the context of HPV+ disease is an area of active research. This includes the presence and extent of extranodal extension, and the number of involved nodes.

ORPH-A
2 OF 2

Omitting systemic therapy and administering RT alone is a category 2B option for patients with p16-positive cT0–2, cN0–1 disease (single node ≤3 cm) who have extranodal extension following surgery. For patients with positive or close margins, reresection (if feasible), RT, and systemic therapy/RT are treatment options.[84] For patients with other risk features such as pT3 or pT4 primary, one positive node >3 cm or multiple positive nodes, nodal disease in levels IV or V, perineural invasion, vascular invasion, or lymphatic invasion, adjuvant treatment options include RT or systemic therapy/RT (category 2B) (see ORPHPV-1 and ORPHPV-2, pages 226 and 227, respectively).

For locally advanced resectable disease (T0–2cN1 [single node >3 cm, or ≥2 ipsilateral nodes ≤6 cm] or T0–2N2, or T3N0–3, or T4, treatment recommendations include concurrent systemic therapy/RT[84,85] and resection of the primary and neck dissection (with appropriate adjuvant therapy [systemic therapy/RT or RT]), in addition to enrollment in clinical trials (see ORPHPV-3 and ORPHPV-4, pages 228 and 229, respectively). As with early-stage disease, tumors at or approaching the midline should be strongly considered for bilateral treatment of the neck. The panel asserts that concurrent systemic therapy/RT is preferred in patients with locoregionally advanced HPV-positive disease who have clinical evidence of fixed or matted nodes or obvious extranodal extension, because surgery is not recommended for these patients. Induction chemotherapy (followed by RT or systemic therapy/RT) is listed as a treatment option for these patients,[60,62,86] but is a category 3 option due to lack of consensus among NCCN Member Institutions. Panel concerns are based on absence of consistent benefit of induction chemotherapy in randomized clinical trials and concerns that use of better-tolerated—but potentially less effective—concurrent regimens or poorer patient compliance with RT may compromise outcomes. For more detail, see the Discussion section in the full version of the NCCN Guidelines for Head and Neck Cancers (available at NCCN.org). Patients with cN2–3 disease who are treated with initial surgery have a high likelihood of extranodal extension, which warrants adjuvant systemic therapy/RT treatment. Triple modality management is associated with increased toxicity. Beginning treatment with concurrent systemic therapy/RT may help decrease the need for triple modality therapy and additional treatment-induced morbidity. Therefore, definitive concurrent systemic therapy/RT is preferred over up-front surgery for p16-positive cT4 or cN3 oropharyngeal cancer (see ORPHPV-4, page 229).

In 3 randomized phase III trials, cetuximab + RT was compared with cisplatin + RT as a deintensification treatment strategy for HPV-positive locally advanced oropharyngeal cancer, but cetuximab + RT proved to be inferior to cisplatin (in terms of OS) and was not better tolerated.[87,88] In the RTOG 1016 noninferiority trial, 849 patients with locally advanced HPV-positive oropharyngeal cancer were randomized to receive accelerated intensity-modulated RT (IMRT) with either cetuximab or cisplatin.[87] After a median follow-up of 4.5 years, the cetuximab arm did not meet the criterion for noninferiority (based on 5-year OS). Five-year OS was 77.9% for the cetuximab arm and 84.6% for the cisplatin arm. PFS and risk of locoregional failure were significantly worse in the cetuximab arm compared with the cisplatin arm (HR, 1.72; 95% CI, 1.29–2.29; $P<.001$ for PFS; HR, 2.05; 95% CI, 1.35–3.10; $P<.001$ for locoregional failure), with 5-year PFS and locoregional failure rates being 67.3% and 17.3% for the cetuximab arm, and 78.4% and 9.9% for the cisplatin arm, respectively. In the randomized phase III De-ESCALaTE HPV trial, cetuximab + RT was compared with cisplatin + RT in 334 patients with locally advanced p16-positive oropharyngeal squamous cell carcinoma.[88] Patients treated with cisplatin + RT had significantly better 2-year OS (97.5% vs 89.4%, respectively; HR, 5.0; 95% CI, 1.7–14.7; $P=.001$) and a lower recurrence rate (6.0% vs 16.1%, respectively; HR, 3.4; 95% CI, 1.6–7.2; $P<.001$) than those treated with cetuximab + RT. In the multicenter TROG 12.01 trial, 189 patients with intermediate-risk HPV-positive oropharyngeal cancer were randomized to receive 70 Gy RT with either weekly cisplatin or cetuximab.[89] The 3-year failure-free survival was 93% in the RT/cisplatin arm and 80% in the RT/cetuximab arm ($P=.015$). These 3 phase III trials demonstrated that cetuximab and RT was inferior to cisplatin and RT in patients with HPV-positive oropharyngeal cancer.[87–89] When concurrent systemic therapy/RT is recommended for treatment of locoregionally advanced p16-positive cancer of the oropharynx, the panel asserts that high-dose cisplatin is the preferred systemic agent, although weekly cisplatin is also an option. An NRG Oncology trial is currently in progress for comparing high-dose cisplatin to weekly cisplatin in locally advanced SCCHN (ClinicalTrials.gov identifier: NCT05050162).

RT Fractionation

IMRT is preferred for radiation treatment of oropharynx cancer, because it is associated with decreased toxicity.[90,91] There is an ongoing randomized trial comparing IMRT with intensity-modulated proton therapy in oropharyngeal cancer (ClinicalTrials.gov identifier: NCT01893307). A fractionation schedule of 66 to 70 Gy at 2 Gy/fraction daily (Monday–Friday) for 6 to 7 weeks is recommended for patients with gross disease. Hypofractionation, hyperfractionation, or accelerated fractionation is acceptable in patients with early-stage oropharyngeal cancer and may be associated with improved locoregional control.[84,92] For elective nodal treatment, a biologically equivalent dose of approximately 40 to 50 Gy in 2 Gy/fraction is recommended.[84,93] The complete list of recommended schedules for radiation treatment of p16-positive oropharynx cancer are shown in the algorithm (see "Principles of Radiation Therapy," ORPH-A 1 and 2, pages 230 and 231). Despite the evidence that RT dose deintensification may improve long-term function while preserving PFS in patients with p16-positive disease,[67–69,73] more studies are needed in this area. The majority of clinical trials in this space have been single-arm phase II and need to be compared with the standard of care in randomized trials. Currently, enrollment of patients with low-risk HPV-positive oropharyngeal cancer is in progress for the randomized phase II/III NRG HN-005 trial, which will compare de-escalated 60 Gy with cisplatin, 60 Gy with nivolumab, and 70 Gy with cisplatin (NCT03952585).

Summary

The incidence of HPV-positive oropharyngeal cancer is increasing in the United States, and patients with locally advanced HPV-positive SCCHN have improved outcomes relative to patients with HPV-negative tumors. The NCCN Guidelines for Head and Neck Cancers recommend tumor HPV testing in all patients with oropharyngeal cancer. Treatment deintensification (eg, dose-reduced RT) is an active area of research with promising preliminary results. However, definitive data from randomized phase III trials must be available before RT deintensification for HPV-positive cancers is considered a standard option. Ongoing clinical trials specific to this unique subset of head and neck cancers are anticipated to further inform these NCCN Guidelines.

References

1. Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612–619.
2. 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.

3. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA 2012;307:693–703.
4. Näsman 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.
5. 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.
6. Snow AN, Laudadio J. Human papillomavirus detection in head and neck squamous cell carcinomas. Adv Anat Pathol 2010;17:394–403.
7. 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.
8. Lu DJ, Luu M, Mita A, et al. Human papillomavirus-associated oropharyngeal cancer among patients aged 70 and older: Dramatically increased prevalence and clinical implications. Eur J Cancer 2018;103:195–204.
9. Tota JE, Best AF, Zumsteg ZS, et al. Evolution of the oropharynx cancer epidemic in the United States: moderation of increasing incidence in younger individuals and shift in the burden to older individuals. J Clin Oncol 2019;37:1538–1546.
10. 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.
11. 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.
12. 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.
13. 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. JAMA Oncol 2016;2:599–606.
14. LeConte BA, Szaniszlo P, Fennewald SM, et al. Differences in the viral genome between HPV-positive cervical and oropharyngeal cancer. PLoS One 2018;13:e0203403.
15. Steinau M, Saraiya M, Goodman MT, et al. Human papillomavirus prevalence in oropharyngeal cancer before vaccine introduction, United States. Emerg Infect Dis 2014;20:822–828.
16. da Silva RL, da Silva Batista Z, Bastos GR, et al. Role of HPV 16 variants among cervical carcinoma samples from Northeastern Brazil. BMC Womens Health 2020;20:162.
17. Gillison ML, Akagi K, Xiao W, et al. Human papillomavirus and the landscape of secondary genetic alterations in oral cancers. Genome Res 2019;29:1–17.
18. Chaturvedi AK, Graubard BI, Broutian T, et al. Effect of prophylactic human papillomavirus (HPV) vaccination on oral HPV infections among young adults in the United States. J Clin Oncol 2018;36:262–267.
19. Chaturvedi AK, Graubard BI, Broutian T, et al. Prevalence of oral HPV infection in unvaccinated men and women in the United States, 2009-2016. JAMA 2019;322:977–979.
20. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915–1927.
21. Beachler DC, Kreimer AR, Schiffman M, et al. Multisite HPV16/18 vaccine efficacy against cervical, anal, and oral HPV infection. J Natl Cancer Inst 2015;108:108.
22. Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med 2020;383:1340–1348.
23. 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.
24. 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.
25. 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.
26. 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.
27. Fakhry C, Zhang Q, Nguyen-Tân PF, et al. Development and validation of nomograms predictive of overall and progression-free survival in patients with oropharyngeal cancer. J Clin Oncol 2017;35:4057–4065.
28. Fullerton ZH, Butler SS, Mahal BA, et al. Short-term mortality risks among patients with oropharynx cancer by human papillomavirus status. Cancer 2020;126:1424–1433.
29. Ren J, Yang W, Su J, et al. Human papillomavirus and p16 immunostaining, prevalence and prognosis of squamous carcinoma of unknown primary in the head and neck region. Int J Cancer 2019;145:1465–1474.
30. 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.
31. 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.
32. Coordes A, Lenz K, Qian X, et al. Meta-analysis of survival in patients with HNSCC discriminates risk depending on combined HPV and p16 status. Eur Arch Otorhinolaryngol 2016;273:2157–2169.
33. 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.
34. 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.
35. 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.
36. Lassen P, Lacas B, Pignon JP, et al. Prognostic impact of HPV-associated p16-expression and smoking status on outcomes following radiotherapy for oropharyngeal cancer: the MARCH-HPV project. Radiother Oncol 2018;126:107–115.
37. 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.
38. 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.
39. 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.
40. Huang SH, O'Sullivan B, Su J, et al. Prognostic importance of radiologic extranodal extension in HPV-positive oropharyngeal carcinoma and its potential role in refining TNM-8 cN-classification. Radiother Oncol 2020;144:13–22.
41. 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.
42. Cantley RL, Gabrielli E, Montebelli F, et al. Ancillary studies in determining human papillomavirus status of squamous cell carcinoma of the oropharynx: a review. Pathol Res Int 2011;2011:138469.
43. Prigge ES, Arbyn M, von Knebel Doeberitz M, et al. Diagnostic accuracy of $p16^{INK4a}$ immunohistochemistry in oropharyngeal squamous cell carcinomas: a systematic review and meta-analysis. Int J Cancer 2017;140:1186–1198.
44. Lang Kuhs KA, Wood CB, Wiggleton J, et al. Transcervical sonography and human papillomavirus 16 E6 antibodies are sensitive for the detection of oropharyngeal cancer. Cancer 2020;126:2658–2665.
45. 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.
46. 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.
47. Begum S, Gillison ML, Nicol TL, et al. 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.
48. Lewis JS Jr, Beadle B, Bishop JA, et al. Human papillomavirus testing in head and neck carcinomas: guideline from the College of American Pathologists. Arch Pathol Lab Med 2018;142:559–597.
49. 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.
50. 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.

51. Gillison ML. Human papillomavirus and oropharyngeal cancer stage. J Clin Oncol 2016;34:1833–1835.
52. Amin M, Edge S, Greene F, et al. AJCC Cancer Staging Manual, 8th edition. New York, NY: Springer; 2017.
53. 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.
54. 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.
55. Mehanna H. Update on de-intensification and intensification studies in HPV. Recent Results Cancer Res 2017;206:251–256.
56. Mehanna H, Rischin D, Wong SJ, et al. De-escalation after DE-ESCALATE and RTOG 1016: a Head and Neck Cancer InterGroup Framework for future de-escalation studies. J Clin Oncol 2020;38:2552–2557.
57. 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.
58. 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.
59. 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.
60. Adelstein DJ, Ridge JA, Brizel DM, et al. Transoral resection of pharyngeal cancer: summary of a National Cancer Institute Head and Neck Cancer Steering Committee Clinical Trials Planning Meeting, November 6-7, 2011, Arlington, Virginia. Head Neck 2012;34:1681–1703.
61. Hinni ML, Zarka MA, Hoxworth JM. Margin mapping in transoral surgery for head and neck cancer. Laryngoscope 2013;123:1190–1198.
62. Li RJ, Richmon JD. Transoral endoscopic surgery: new surgical techniques for oropharyngeal cancer. Otolaryngol Clin North Am 2012;45:823–844.
63. Cracchiolo JR, Baxi SS, Morris LG, et al. Increase in primary surgical treatment of T1 and T2 oropharyngeal squamous cell carcinoma and rates of adverse pathologic features: National Cancer Data Base. Cancer 2016; 122:1523–1532.
64. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. Lancet Oncol 2019;20:1349–1359.
65. Nichols AC, Theurer J, Prisman E, et al. Randomized trial of radiotherapy versus transoral robotic surgery for oropharyngeal squamous cell carcinoma: long-term results of the ORATOR trial [published online January 7, 2022]. J Clin Oncol, doi:10.1200/JCO.21.01961
66. Palma D, Nichols A. A phase II randomized trial of treatment de-escalation for HPV associated oropharyngeal squamous cell carcinoma: radiotherapy vs trans-oral surgery (ORATOR 2). Presented at the 2021 American Society for Radiation Oncology Annual Meeting; October 24–27, 2021; Chicago, Illinoi. Abstract LBA-2.
67. 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. J Clin Oncol 2017; 35:490–497.
68. Chen AM, Felix C, Wang PC, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. Lancet Oncol 2017;18:803–811.
69. Chera BS, Amdur RJ, Tepper JE, et al. Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2018; 124:2347–2354.
70. Chera BS, Amdur RJ, Green R, et al. Phase II trial of de-intensified chemoradiotherapy for human papillomavirus-associated oropharyngeal squamous cell carcinoma. J Clin Oncol 2019;37:2661–2669.
71. Ma DJ, Price KA, Moore EJ, et al. Phase II evaluation of aggressive dose de-escalation for adjuvant chemoradiotherapy in human papillomavirus-associated oropharynx squamous cell carcinoma. J Clin Oncol 2019;37:1909–1918.
72. Yom SS, Torres-Saavedra P, Caudell JJ, et al. Reduced-dose radiation therapy for HPV-associated oropharyngeal carcinoma (NRG Oncology HN002). J Clin Oncol 2021;39:956–965.
73. Hegde JV, Shaverdian N, Daly ME, et al. Patient-reported quality-of-life outcomes after de-escalated chemoradiation for human papillomavirus-positive oropharyngeal carcinoma: findings from a phase 2 trial. Cancer 2018;124:521–529.
74. Ferris RL, Flamand Y, Weinstein GS, et al. Phase II randomized trial of transoral surgery and low-dose intensity modulated radiation therapy in resectable p16+ locally advanced oropharynx cancer: an ECOG-ACRIN Cancer Research Group Trial (E3311). J Clin Oncol 2022;40:138–149.
75. 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.
76. 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.
77. 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.
78. 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.
79. 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.
80. 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.
81. An Y, Park HS, Kelly JR, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2017;123:2762–2772.
82. Haughey BH, Sinha P. Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. Laryngoscope 2012;122(Suppl 2): S13–33.
83. Freitag J, Wald T, Kuhnt T, et al. Extracapsular extension of neck nodes and absence of human papillomavirus 16-DNA are predictors of impaired survival in p16-positive oropharyngeal squamous cell carcinoma. Cancer 2020;126:1856–1872.
84. Sher DJ, Adelstein DJ, Bajaj GK, et al. Radiation therapy for oropharyngeal squamous cell carcinoma: executive summary of an ASTRO evidence-based clinical practice guideline. Pract Radiat Oncol 2017;7: 246–253.
85. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.
86. Haughey BH, Hinni ML, Salassa JR, et al. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. Head Neck 2011;33:1683–1694.
87. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet 2019;393:40–50.
88. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Lancet 2019;393:51–60.
89. Rischin D, King M, Kenny L, et al. Randomized trial of radiation therapy with weekly cisplatin or cetuximab in low-risk HPV-associated oropharyngeal cancer (TROG 12.01)—a Trans-Tasman Radiation Oncology Group Study. Int J Radiat Oncol Biol Phys 2021;111:876–886.
90. Garden AS, Kies MS, Morrison WH, et al. Outcomes and patterns of care of patients with locally advanced oropharyngeal carcinoma treated in the early 21st century. Radiat Oncol 2013;8:21.
91. Al-Mamgani A, Van Rooij P, Tans L, et al. Toxicity and outcome of intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy for oropharyngeal cancer: a matched-pair analysis. Technol Cancer Res Treat 2013;12:123–130.
92. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333–1338.
93. Deschuymer S, Nevens D, Duprez F, et al. Randomized clinical trial on reduction of radiotherapy dose to the elective neck in head and neck squamous cell carcinoma; update of the long-term tumor outcome. Radiother Oncol 2020;143:24–29.