Head and Neck Cancers, Version 2.2020

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ABSTRACT

Treatment is complex for patients with head and neck (H&N) cancers with specific site of disease, stage, and pathologic findings guiding treatment decision-making. Treatment planning for H&N cancers involves a multidisciplinary team of experts. This article describes supportive care recommendations in the NCCN Guidelines for Head and Neck Cancers, as well as the rationale supporting a new section on imaging recommendations for patients with H&N cancers. This article also describes updates to treatment recommendations for patients with very advanced H&N cancers and salivary gland tumors, specifically systemic therapy recommendations.

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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. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

The complete NCCN Guidelines for Head and Neck Cancers are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

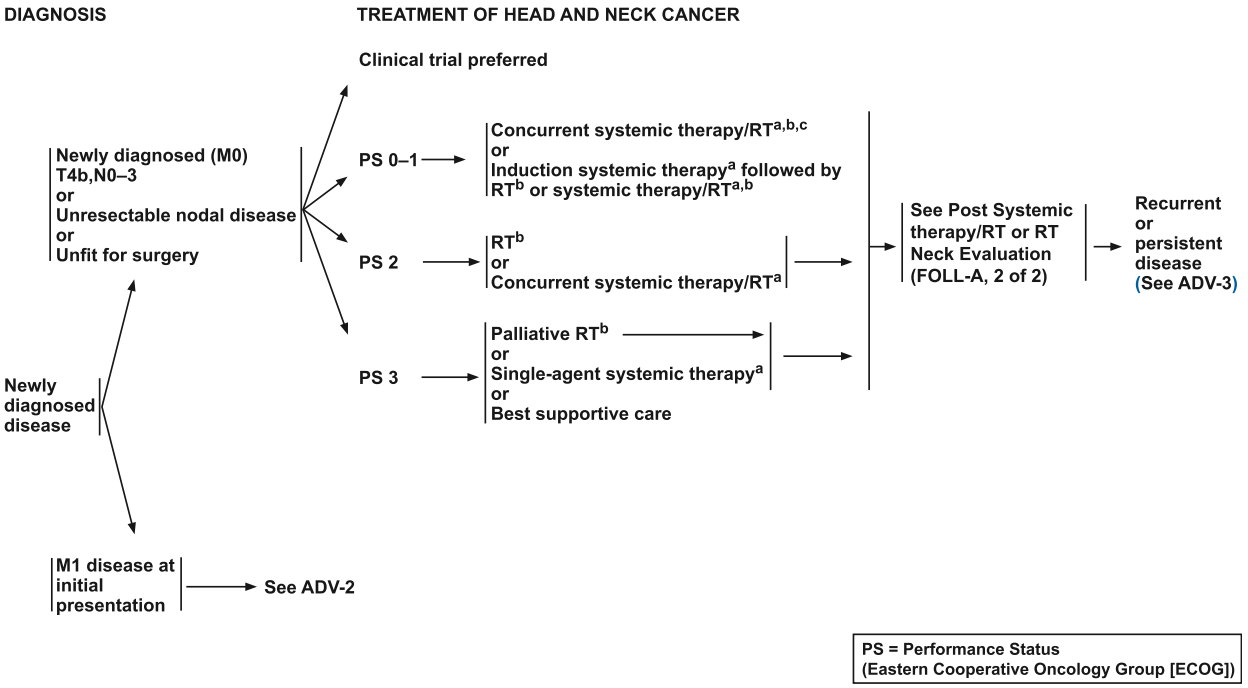
Disclosures for the NCCN Head and Neck Cancers Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Head and Neck Cancers Panel members can be found on page 898. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

Very Advanced Head and Neck Cancer



[a]See Principles of Systemic Therapy (SYST-A).
[b]See Principles of Radiation Therapy (ADV-A).
[c]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (SYST-A).

Overview

The NCCN Guidelines for Head and Neck Cancers address tumors arising in the lip, oral cavity, pharynx, larynx, and paranasal sinuses; occult primary cancer, salivary gland cancer, and mucosal melanoma are also addressed.[1,2] In 2020, it is estimated that about 65,630 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur, which account for about 3.6% of new cancer cases in the United States.[3] An estimated 14,500 deaths from head and neck (H&N) cancers will occur during the same time period.[4] Squamous cell carcinoma or a variant is the histologic type in more than 90% of these tumors.

Alcohol and tobacco abuse are the most common etiologic factors in cancers of the oral cavity, hypopharynx, larynx, and HPV-unrelated oropharynx. Because the entire aerodigestive tract epithelium may be exposed to these carcinogens, patients with H&N cancers are at risk for harboring synchronous primary tumors and developing second primary neoplasms of the H&N, lung, esophagus, and other sites that share these risk factors. The attributable fraction for HPV in newly diagnosed oropharyngeal cancer is estimated at 60%–70% in the United States and parts of the European Union.[5–9] In the case of nasopharyngeal carcinoma, 95% of cases in endemic regions are of differentiated or undifferentiated nonkeratinizing type, which is very closely associated with infection with Epstein-Barr virus.[10–12] In the United States, however, keratinizing types comprise upwards of 40% based on SEER data, although both keratinizing and nonkeratinizing types are found in all ethnicities.[13]

Stage at diagnosis predicts survival rates and guides management in patients with H&N cancers. In general, stage I or II disease defines a relatively small primary tumor with no nodal involvement. Stage III or IV cancers generally include larger primary tumors, which may invade underlying structures and/or spread to regional nodes. Distant metastases are less common at presentation than in lung and esophagus cancers. More advanced TNM stages are associated with worse survival. The 8th edition of the AJCC Cancer Staging Manual included new staging criteria for HPV-related oropharyngeal

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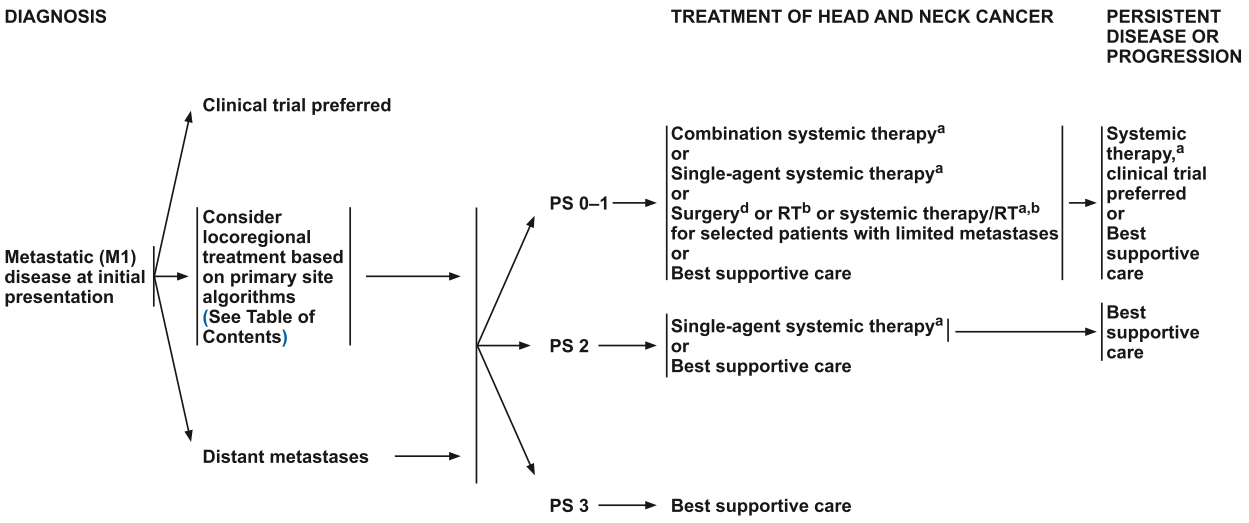

*Available online, in these guidelines, at NCCN.org.

ADV-2

cancer.[14] In these staging criteria, nodal disease could be considered stage I if the nodes are ipsilateral and none larger than 6 cm. Staging of nasopharyngeal cancer is also different from other H&N cancer sites, since the primary treatment of this disease is radiation therapy (RT) with or without chemotherapy.[14] Nasopharyngeal cancers are generally not resected; therefore, the staging for this cancer does not include pathologic classification.

Management Approaches

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). Single-modality treatment with surgery or RT is generally recommended for the approximately 30%–40% of patients who present with early-stage disease (stage I or II). Surgery and RT result in similar survival for many H&N cancers, but surgery is usually preferred for oral cavity and paranasal sinus cancers, while RT with or without chemotherapy is nearly always preferred for all stages of nasopharyngeal carcinoma. 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 RT and less invasive surgery, as well as improving supportive care for patients receiving systemic therapy, 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. When chemotherapy is delivered with radiation, cisplatin is the preferred radiosensitizer.

Participation in clinical trials is a preferred or recommended treatment option in many situations. In formulating these NCCN Guidelines, panel members have tried to make them evidence-based while providing a statement of consensus as to the acceptable range of treatment options. In numerous population-based studies, patients treated at high-volume centers appear to have better outcomes relative to patients treated at low-volume centers.[15–19]

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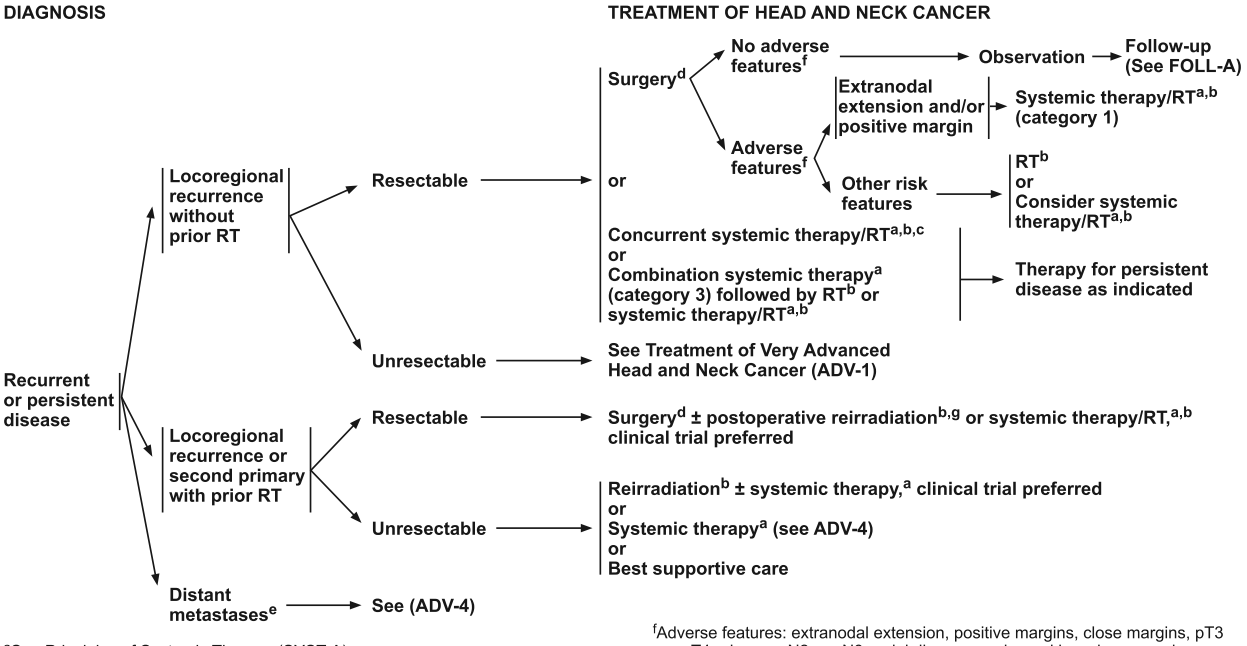

[a]See Principles of Systemic Therapy (SYST-A).
[b]See Principles of Radiation Therapy (ADV-A).
[c]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (SYST-A).
[d]See Principles of Surgery (SURG-A*).
[e]Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A*).
[f]Adverse features: extranodal extension, positive margins, close margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion (See Discussion).
[g]Reirradiation should be limited to a highly select subset of patients (Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clin Oncol 2008;26:5518-5523).

*Available online, in these guidelines, at NCCN.org.

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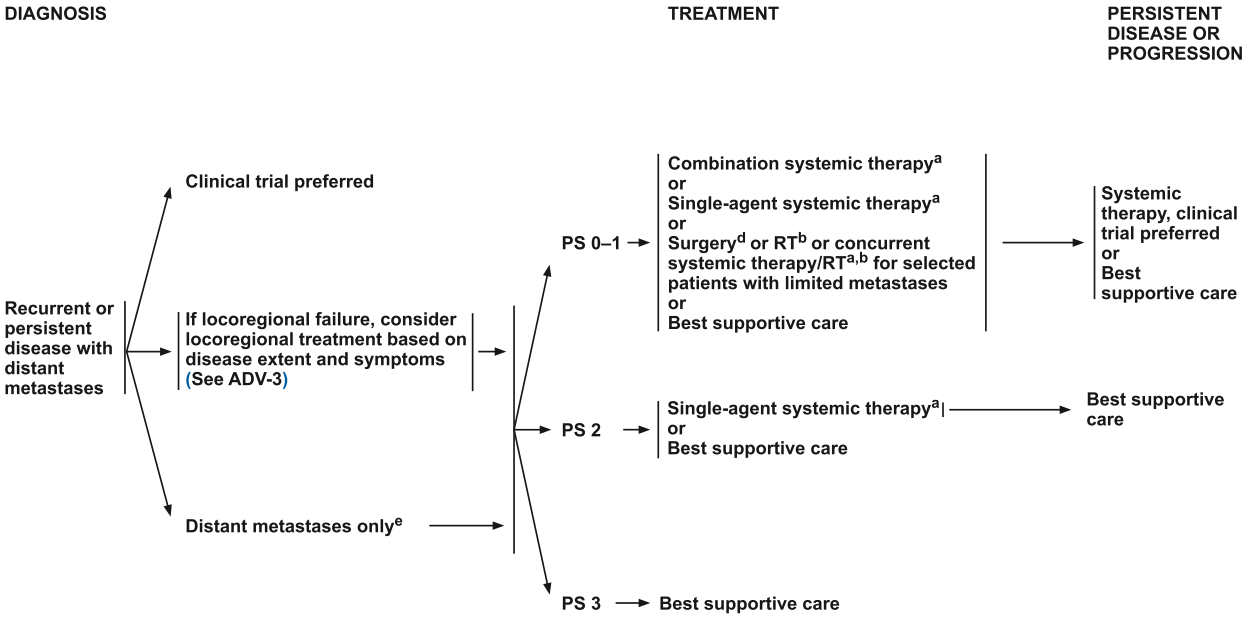
Multidisciplinary Team Involvement

The initial evaluation and development of a plan for treating the patient with H&N cancer requires a multidisciplinary team of health care providers with expertise in caring for these patients.[20,21] Similarly, managing and preventing sequelae after surgery, RT, and systemic therapy (eg, pain, lymphedema and muscle spasm of the neck, xerostomia, dysphagia, speech and swallowing problems, depression) require professionals familiar with the disease.[22–24] Follow-up for these sequelae should include a comprehensive H&N examination and supportive care and rehabilitation (see "Follow-Up Recommendations," page 883).[20] Adequate nutritional support can help to prevent severe weight loss in patients receiving treatment of H&N cancers; therefore, patients should be encouraged to see a registered dietitian at diagnosis and as needed during and after treatment (see "Principles of Nutrition: Management and Supportive Care," in these guidelines at NCCN.org and "Principles of Nutrition and Supportive Care," page 883).[25] Dental care to prevent and treat RT effects should be provided (see "Principles of Dental Evaluation and Management," in these guidelines at NCCN.org and page 886). Evaluation by a speech-language/swallowing therapist before and after treatment is recommended. Patients are at risk for depression from H&N cancer and its sequelae, so screening for depression is advised (see the NCCN Guidelines for Distress Management, available at NCCN.org).[26–29] Fertility/reproductive counseling should be offered to younger patients (see the NCCN Guidelines for Adolescent and Young Adult Oncology, available at NCCN.org). Specific components of patient support and follow-up are listed in the algorithm (see "Team Approach," in these guidelines at NCCN.org). Panel members also recommend referring to the NCCN Guidelines for Palliative Care and Adult Cancer Pain as needed (available at NCCN.org).

Tobacco use is associated with at least 30% of cancer deaths.[30] Therefore, patients' tobacco use history should be assessed. Patients should be encouraged to stop smoking (and remain abstinent) and to modify alcohol consumption if excessive because these habits decrease

Very Advanced Head and Neck Cancer



[a]See Principles of Systemic Therapy (SYST-A).
[b]See Principles of Radiation Therapy (ADV-A).

*Available online, in these guidelines, at NCCN.org.

[d]See Principles of Surgery (SURG-A*).
[e]Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A*).

ADV-4

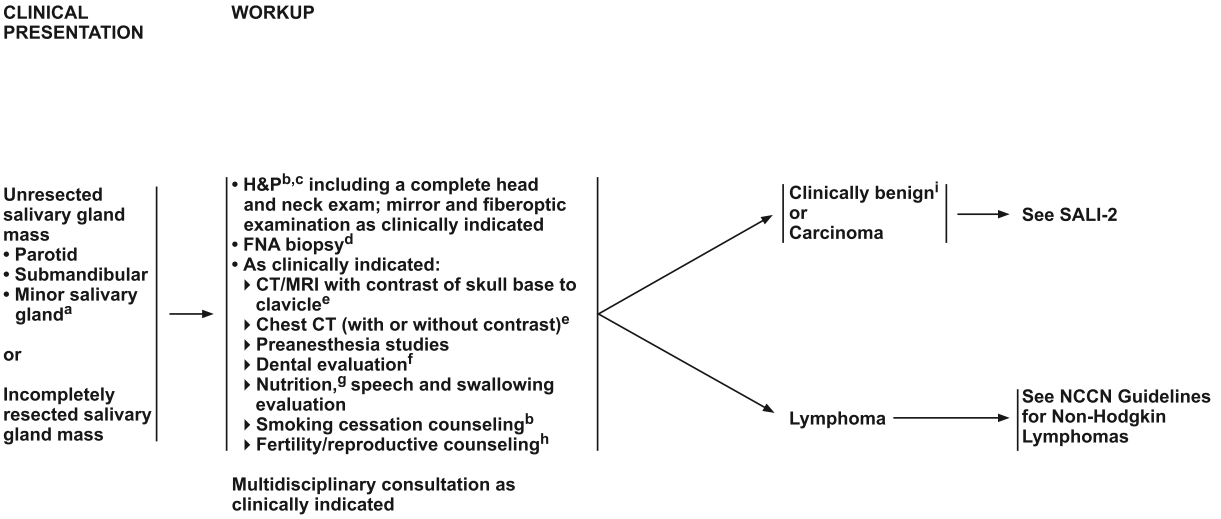
the efficacy of treatment and adversely affect other health outcomes.[31,32] Information on smoking cessation resources and support can be found in the NCCN Guidelines for Smoking Cessation (available at NCCN.org).

Resectable Versus Unresectable Disease

The term *unresectable* has resisted formal definition by H&N cancer specialists. The experience of the surgeon and the support available from reconstructive surgeons, physiatrists, and prosthodontists often strongly influence recommendations, especially in institutions where only a few patients with locally advanced H&N cancers are treated. The NCCN Member Institutions have teams experienced in the treatment of H&N cancers and maintain the multidisciplinary infrastructure needed for reconstruction and rehabilitation. A patient's cancer is deemed unresectable if H&N surgeons at NCCN Member Institutions do not think they can remove the gross tumor on anatomic grounds or if local control is unlikely to be achieved with the use of surgery (even with the addition of RT to the treatment approach). Typically, these unresectable tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery (see "Principles of Surgery," in these guidelines at NCCN.org). Tumor involvement of certain sites is associated with poor prognosis (ie, direct extension of neck disease to involve the external skin; direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae).

Unresectable tumors should be distinguished from inoperable tumors in those patients whose constitutional state precludes an operation (even if the cancer could be readily resected with few sequelae). Additionally, a subgroup of patients will decline surgical management, but their tumors should not be deemed unresectable. In some patients, adequate reconstructive options may be lacking; therefore, the patient's disease is considered functionally unresectable. Examples include bilateral orbital exenteration or exenteration in the only seeing eye, extensive mandibular resection without reconstruction options, or total pharyngectomy when reconstitution of the alimentary tract is not feasible.

Salivary Gland Tumors



[a] Site and stage determine therapeutic approaches.
[b] H&P should include documentation and quantification (pack years smoked) of tobacco use history. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support, refer to the Patient/Provider Smoking Cessation Resources in the NCCN Guidelines for Smoking Cessation†.
[c] Screen for depression (See NCCN Guidelines for Distress Management†).
[d] Image-guided (US or CT) needle biopsy of cystic neck nodes may offer better diagnostic yield than FNA by palpation alone for initial diagnosis in this setting.
[e] See Principles of Imaging (IMG-A*).
[f] See Principles of Dental Evaluation and Management (DENT-A*).
[g] See Principles of Nutrition: Management and Supportive Care (NUTR-A*).
[h] See fertility and reproductive endocrine considerations in the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology†.
[i] Characteristics of a benign tumor include mobile superficial lobe, slow growth, painless, V and/or VII intact, and no neck nodes.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

SALI-1

Though these are rare occurrences, the impact on quality of life and the need for continual supportive care are significant and open ended. Although local and regional disease may be surgically treatable, patients with distant metastases are usually treated as though the primary tumor was unresectable. Thus, patient choice or physician expectations regarding cure and morbidity will influence or determine treatment. Patients with resectable tumors who can also be adequately treated without surgery represent a very important group. Definitive treatment with RT alone or RT combined with systemic therapy may represent equivalent or preferable approaches to surgery in these individuals. Although such patients may not undergo surgery, their tumors should not be labeled as unresectable. Their disease is usually far less extensive than those with disease that truly cannot be removed.

Comorbidity and Quality of Life

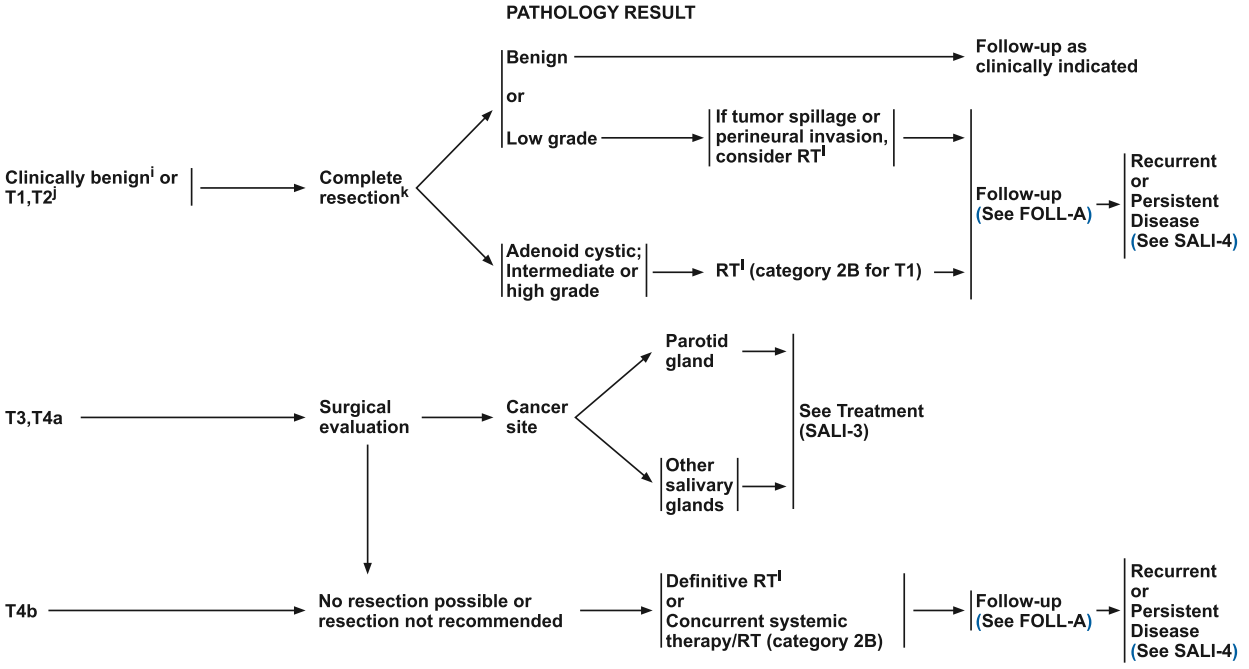
Comorbidity

Comorbidity refers to the presence of concomitant disease (in addition to H&N cancers) that may affect diagnosis, treatment, and prognosis.[33,34] Documentation of comorbidity is important to facilitate optimal treatment selection. Comorbidity is known to be a strong independent predictor for mortality in patients with H&N cancers,[35–38] and comorbidity also influences costs of care, utilization, and quality of life.[39–41] Traditional indices of comorbidity include the Charlson Comorbidity Index[42] and the Kaplan-Feinstein Index and its modifications.[34,43] The Adult Comorbidity Evaluation-27 (ACE-27) is a validated instrument for assessing comorbidity in numerous cancer types including H&N cancers.[44] An important consideration when interpreting published clinical trial data are the applicability of the results to patients with significant comorbidities, who may have been ineligible/excluded from such studies.

Quality of Life

Health-related quality-of-life issues are important in H&N cancers. These tumors affect basic physiologic functions (ie, the ability to chew, swallow, and breathe), the senses (ie, taste, smell, hearing), and uniquely human

Salivary Gland Tumors



[i]Characteristics of a benign tumor include mobile superficial lobe, slow growth, painless, V and/or VII intact, and no neck nodes.
[j]If incidental N+ disease is present go to SALI-3.
[k]Resection of a clinically benign tumor includes: no enucleation of lateral lobe and intraoperative communication with pathologist if indicated.
[l]See Principles of Radiation Therapy (SALI-A).

SALI-2

characteristics (ie, appearance, voice). *Health status* describes an individual's physical, emotional, and social capabilities and limitations. *Function* and *performance* refer to how well an individual is able to perform important roles, tasks, or activities. *Quality of life* differs, because the central focus is on the value (determined by the patient alone) that individuals place on their health status and function.[45]

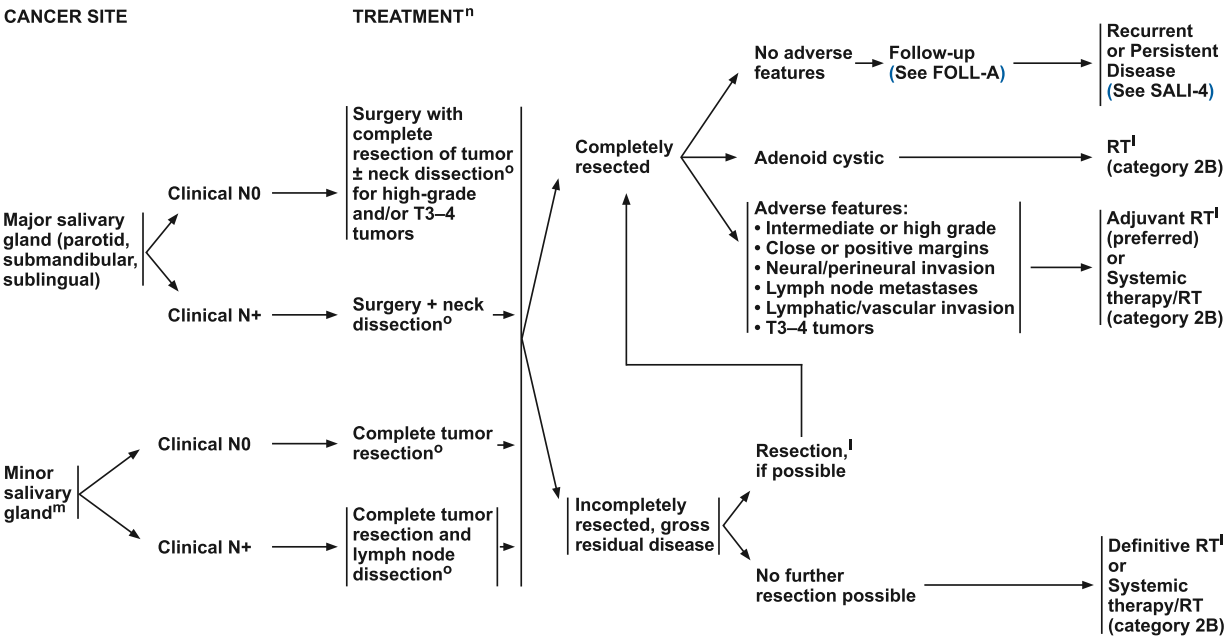
Patient-completed scales should be used to measure quality of life.[46] Three validated and accepted measures for H&N cancer–specific issues are (1) the University of Washington Quality of Life Questionnaire[47]; 2) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module[48]; and 3) the Functional Assessment of Cancer Therapy Head and Neck scale.[49] The Performance Status Scale is a clinician-rated performance scale that is widely used for patients with H&N cancers.[50]

Imaging of Head and Neck Cancers

Appropriate selection and use of imaging studies is crucial for proper management of patients with head and neck cancers. Initial imaging of the primary site is done with CT and/or MRI. MRI is generally preferred over CT in patients with cranial nerve symptoms or to evaluate cranial nerve involvement or tumors that encroach on the skull base. CT, conversely, is complementary to MRI for evaluation of bony erosion or cartilage invasion that may occur with some H&N tumors. In patients with oral cavity cancer with bone involvement, MRI is needed to evaluate the extent of bone marrow invasion, while CT may be appropriate to evaluate cortical bone erosion or periosteal invasion. In patients with sinonasal tumors, MRI is useful for differentiating tumor extent from obstructed sinuses or secretions and to evaluate intracranial/dural involvement. Evaluation of lymph node metastases can be done with either CT or MRI, depending on the primary site, although both have lower accuracy as compared with FDG-PET/CT.[51] Ultimately, choosing CT or MRI should be driven by the information desired; routinely ordering both may not be indicated.

There is evidence supporting the superiority of FDG-PET/CT for detecting locoregional nodal and distant

Salivary Gland Tumors



[l]See Principles of Radiation Therapy (SALI-A).
[m]For submandibular and sublingual gland tumors, complete gland and tumor resection is recommended.
[n]The facial nerve should be preserved if possible; strongly consider referral to a specialized center with reconstructive expertise.
[o]See Principles of Surgery (SURG-A*).

*Available online, in these guidelines, at NCCN.org.

SALI-3

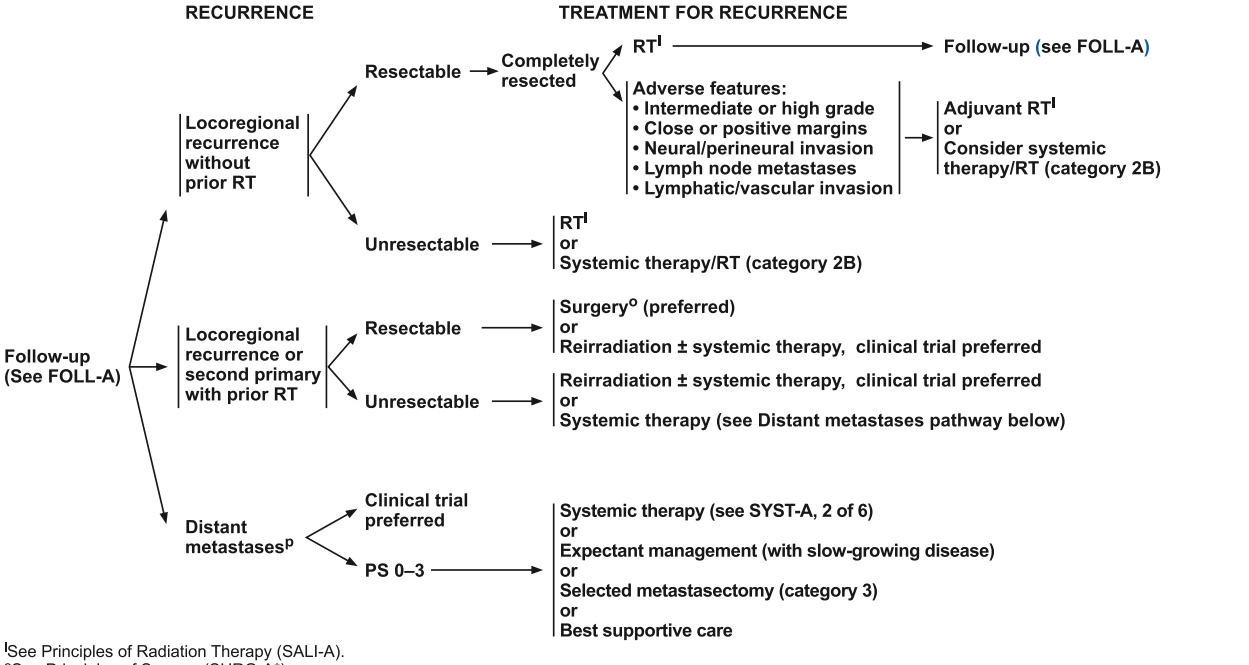
metastases in patients with H&N cancers. A meta-analysis including 24 studies with 1,270 patients with newly diagnosed H&N cancer showed sensitivity and specificity values of 91% and 87%, respectively, for detection of regional nodal metastasis by FDG-PET/CT.[52] In the analysis of per-neck-level data (13 studies), sensitivity was 84%, compared with 63% for CT and/or MRI. Two meta-analyses have shown that sensitivity of FDG-PET/CT for detection of cervical lymph node involvement may be lower in patients with clinically node-negative H&N squamous cell carcinoma (HNSCC) (50%–58%).[53,54] A meta-analysis including 10 studies showed that PET/CT had a sensitivity value of 89% and a specificity value of 98% for detecting bone metastases in patients with H&N cancer.[55] In a prospective cohort study including 307 patients with oral, pharyngeal, or laryngeal cancer, FDG-PET/CT detected distant metastasis more often than chest X-ray/H&N MRI ($P<.001$) and chest CT/H&N MRI ($P=.02$).[56] However, if there is concern about metastasis to a specific anatomic area, then directed CT or MRI may also be done (eg, contrast-enhanced chest CT to evaluate pulmonary metastases and/or mediastinal lymph node involvement; contrast-enhanced brain MRI for evaluation of brain metastases or skull base invasion). H&N cancers rarely metastasize to the brain by a hematogenous route. Therefore, routinely ordering a full brain study as part of the initial imaging workup is not routine.

For patients who are dentulous and expected to receive postoperative RT, a panoramic dental X-ray should be completed before treatment as part of the dental evaluation (see "Principles of Dental Evaluation and Management," in these guidelines at NCCN.org and page 886).

Short-Term Evaluation of Locoregionally Advanced Disease

Serial imaging may be part of response assessment. Which modality is best suited for follow-up should be carefully considered. It is unlikely all 3 modalities (CT, MRI, FDG PET/CT) will be needed, because this may add cost and inconvenience without significant added value.

Salivary Gland Tumors



[I]See Principles of Radiation Therapy (SALI-A).
[O]See Principles of Surgery (SURG-A*).
[P]For salivary ductal carcinomas and adenocarcinomas, check androgen receptor (AR) status and HER2 status prior to treatment for distant metastases. Check NTRK status for mammary analog secretory carcinoma (MASC).

PS = Performance Status (ECOG)

*Available online, in these guidelines, at NCCN.org.

SALI-4

Patients treated with induction chemotherapy may receive imaging with CT or MRI after 2 or 3 cycles of induction. If there is high concern for distant metastasis, chest CT or FDG-PET/CT may be needed to evaluate whether to proceed to the planned definitive local therapy.

For patients with locoregionally advanced disease who have undergone surgery, postoperative imaging is recommended if there are signs of early recurrence, or for patients considered at high risk for early recurrence. This may be needed to evaluate whether to proceed to the planned adjuvant radiation-based therapy and/or to determine targets and dosing of radiation in case of unexpected recurrence. Patients with positive margins, advanced T or N stage, or oral cavity cancers are at particular risk for rapid recurrence after surgery.[57]

After definitive-intent treatment completion, the panel generally recommends imaging 3 or 4 months after the end of treatment, or as early as 4 to 8 weeks after definitive treatment if there is concern about an incomplete treatment response. Of note, proximity to recent treatment can complicate interpretation of radiographic studies, and communication with the interpreting radiologist is important to distinguish recurrent disease from posttreatment effect. PET scans can be particularly difficult to interpret at earlier time points.

Careful and regular follow-up examinations are recommended so that any local or regional recurrence is detected early. After RT-based treatment, evaluation with imaging (ie, CT and/or MRI with contrast, or preferably, FDG PET/CT) guides the use of neck dissection (see "Follow-Up Recommendations: Post Systemic Therapy/RT or RT Neck Evaluation," FOLL-A 2 of 2, page 884).[58–62] A meta-analysis including 5 studies with 359 patients showed that the sensitivity and specificity for FDG-PET/CT to detect local residual or recurrent disease were 81% and 90%, respectively, and 73% and 89%, respectively, for detection of nodal residual or recurrent disease.[63] If PET/CT is used for follow-up, the first scan should be performed at a minimum of 12 weeks after treatment to reduce the false-positive rate.[51,63–65] PET/CT surveillance in patients with advanced nodal disease who received

Salivary Gland Tumors

PRINCIPLES OF RADIATION THERAPY[1,2,3]

DEFINITIVE:
RT Alone or Concurrent Systemic Therapy/RT
- **Photon or photon/electron therapy or highly conformal radiation therapy techniques**
- **PTV:**
  - **High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary and at the high-risk level lymph node(s)]**
    - ◊ **Fractionation: 66 Gy (2.0 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[4]**
  - **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)[5]**

POSTOPERATIVE RT:
RT Alone or Concurrent Systemic Therapy/RT
- **Preferred interval between resection and postoperative RT is ≤6 weeks**
- **Photon or photon/electron therapy**
- **PTV**
  - **High risk: Adverse features such as positive margins (see SALI-3)**
    - ◊ **60–66 Gy (2.0 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) to 54–63 Gy (1.6–1.8 Gy/fraction)[5]**

Either IMRT or 3D conformal RT is recommended. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.

[1]See Radiation Techniques (RAD-A*) and Discussion.
[2]Neutron therapy was historically considered a promising solution for unresectable salivary gland cancers, but this therapy is currently offered at only one center in the United States. Pfister DG, Spencer S, Brizel DM, et al. NCCN Head and Neck Cancers, Version 1.2015. J Natl Compr Canc Netw 2015;13:847-855.
[3]In general, the reirradiated population of head and neck cancer patients described in current literature represents a diverse but highly selected group of patients treated in centers where there is a high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment is curative and surgery is not an option, reirradiation strategies can be considered for patients who: develop locoregional failures or second primaries at ≥6 months after the initial radiotherapy; can receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully analyzed through review of dose-volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy. For reirradiation dosing, see Radiation Techniques (RAD-A*). Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)
[4]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.
[5]Suggest 44–50 Gy in 3D conformal RT and sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).

*Available online, in these guidelines, at NCCN.org.

SALI-A

systemic therapy/RT yielded a comparable survival rate and quality of life and may be more cost-effective, relative to planned neck dissection.[66,67] Care should be taken regarding the timing and interpretation of PET studies, as false positive results may occur due to recent infection or treatment-related inflammation.

Note that a *complete clinical response* (ie, clinically negative) may be defined as no visible or palpable evidence of residual neck disease and no concerning findings on CT or MRI (ie, the absence of either focally abnormal lymph nodes or large nodes)[58,68]; a complete pathologic response requires pathologic confirmation. If a complete clinical response to RT-based treatment has been achieved, then the panel recommends observing the patient.[58,68,69] In patients who have a clinically negative neck, PET/CT is associated with negative predictive values ranging from 97% to 100%.[70–72] Panel members also concur that any patient with residual disease after RT-based treatment should be considered for surgical resection for refractory disease, including a neck dissection if indicated.[58] If the residual, persistent, or progressing disease is unresectable, then these patients should receive systemic therapy and/or RT as described for recurrent or persistent disease in the algorithm (see "Recurrent or persistent disease," page 876 and "Recurrent or persistent disease with distant metastases", page 877). For patients with equivocal PET/CT scan results in the neck, a prospective study suggests that a repeat PET/CT scan 4 to 6 weeks later may help identify those patients who can be safely observed without surgery to the neck.[73] These patients may also continue to be observed if the clinical examination is reassuring.

Long-Term Evaluation of Recurrent Disease

Recurrences in patients with head and neck cancer tend to occur in the first 3 years after treatment, with more occurring earlier rather than later in this interval. There is little evidence to support imaging surveillance in the long-term (ie, more than 6 months after treatment) in patients who have negative imaging results,[65,74] though delayed or late recurrences are more common in patients with HPV-related H&N cancer.[75] A meta-analysis including

FOLLOW-UP RECOMMENDATIONS[a]
(based on risk of relapse, second primaries, treatment sequelae, and toxicities)

- **H&P exam (including a complete head and neck exam; and mirror and fiberoptic examination):[b]**
  - **Year 1, every 1–3 mo**
  - **Year 2, every 2–6 mo**
  - **Years 3–5, every 4–8 mo**
  - **>5 years, every 12 mo**
- **Imaging (See Principles of Imaging, IMG-A*)**
- **Thyroid-stimulating hormone (TSH) every 6–12 mo if neck irradiated.**
- **Dental evaluation[c] for oral cavity and sites exposed to significant intraoral radiation treatment.**
- **Consider EBV DNA monitoring for nasopharyngeal cancer (category 2B).**
- **Supportive care and rehabilitation:**
  - **Speech/hearing and swallowing evaluation[d] and rehabilitation as clinically indicated.**
  - **Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is stabilized.[d]**
  - **Ongoing surveillance for depression (See NCCN Guidelines for Distress Management†).**
  - **Smoking cessation[e] and alcohol counseling as clinically indicated.**
- **Integration of survivorship care and care plan within 1 year, complementary to ongoing involvement from a head and neck oncologist (See NCCN Guidelines for Survivorship†).[f]**

[a]Most recurrences are reported by the patient.
[b]For mucosal melanoma and paranasal sinus cancers, a physical exam should include endoscopic inspection for paranasal sinus disease.
[c]See Principles of Dental Evaluation and Management (DENT-A*).
[d]See Principles of Nutrition: Management and Supportive Care (NUTR-A*).
[e]All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support, refer to the Patient/Provider Smoking Cessation Resources in the NCCN Guidelines for Smoking Cessation†.
[f]Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. CA Cancer J Clin 2016;66:203-239.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

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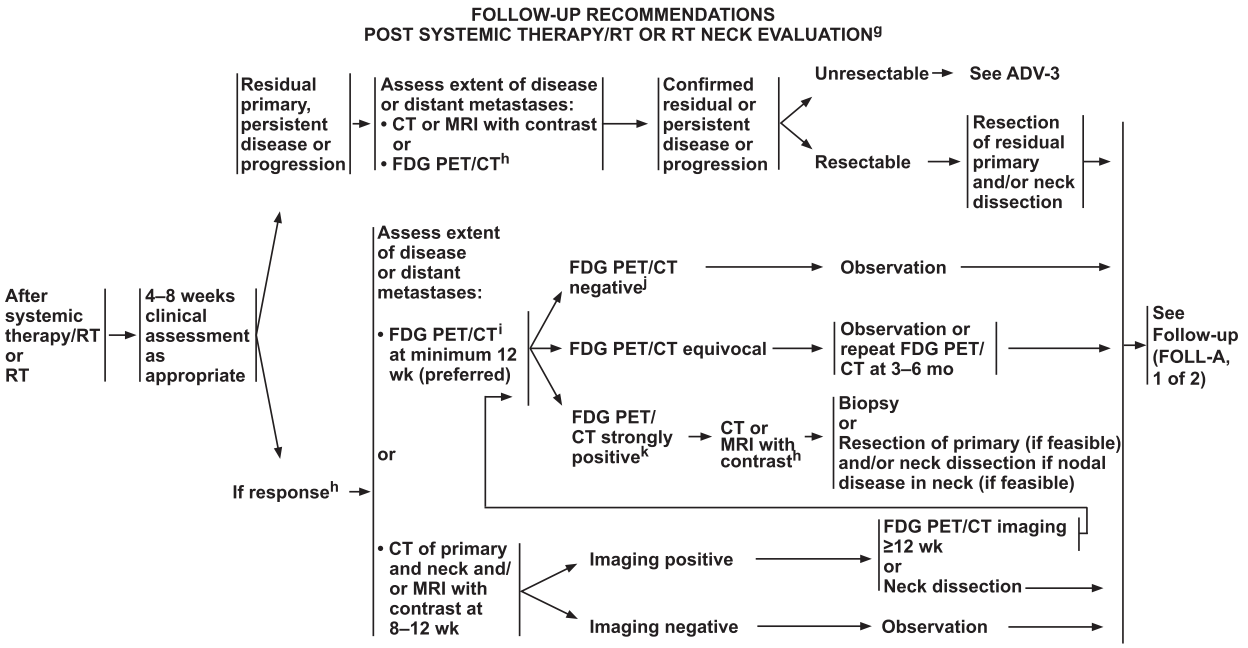
7 studies with 577 scans showed that FDG PET/CT showed high sensitivity (92%) and specificity (91%) values for detection of H&N cancer recurrence 12 months after treatment.[76] However, a retrospective study including 1,114 patients with H&N cancer showed that PET/CT scans conducted at 12 and 24 months after treatment completion become less equivocal with time.[74] Further, among patients with negative 3-month scans, no significant differences in subsequent survival outcomes were seen in patients whose recurrences were detected through PET/CT versus those with clinically detected recurrences. Despite this, the danger of distant metastasis from occult or asymptomatic disease should be acknowledged. A single-institution retrospective study including 123 patients with treated H&N cancer showed that asymptomatic lesions were detected in 20% of patients, with half of these being thoracic lesions.[77]

H&N cancer treatment can result in fibrosis and altered anatomy, which frequently leads to challenges in physical examination that may be assisted by follow-up imaging. Ultimately, the plan for long-term surveillance should take into account tumor site, stage, prognostic factors, presence of symptoms, and changes based on clinical exam. Neck ultrasound, which is widely available, inexpensive, safe, and accurate, may be used to evaluate suspected nodal disease.[51] For areas difficult to visualize by clinical examination (ie, due to anatomy or areas obscured by treatment change), routine annual imaging using the pretreatment imaging modality (usually CT or MRI) may be indicated. The impact of annual screening for lung metastasis or synchronous lung cancer in patients with a heavy smoking history is an area in need of investigation. Annual chest CT should be considered for these patients. Many clinicians obtain chest X-ray for lung screening, but this is not supported by strong evidence due to limited sensitivity[78,79] (see NCCN Guidelines for Lung Cancer Screening, available at NCCN.org).

Principles of Nutrition and Supportive Care

The "Principles of Nutrition" section in the guidelines for online (available at NCCN.org) outlines nutritional management and supportive care for patients with H&N cancers who are prone to weight loss, which can often be severe, as a result of treatment-related toxicity, disease, and health behaviors such as poor nutritional habits.[22,80,81] Patients with H&N cancers are also at risk for dehydration.



[g]Adapted with permission from Kutler DI, Patel SG, Shah JP. The role of neck dissection following definitive chemoradiation. Oncology 2004;18:993-998.
[h] See Principles of Imaging (IMG-A*).
[i]If an FDG PET/CT is performed and negative for suspicion of persistent cancer, further cross-sectional imaging is optional.
[j]PET negative = No or low-grade uptake, felt not suspicious for disease.
[k]PET positive = PET suspicious for disease.

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The multidisciplinary expertise of a registered dietitian and a speech-language/swallowing therapist should be used throughout the continuum of care.

Patients who have had significant weight loss (5% body weight loss over 1 month, or 10% body weight loss over 6 months) need nutritional evaluation and close monitoring of their weight to prevent further weight loss.[82,83] In addition, all patients should receive nutritional evaluation before and after treatment to assess the need for interventions (eg, enteral support via feeding tubes).[84–86] Patients are also at risk for problems with speech. Treatment and/or the progression of their disease may cause deterioration in their ability to speak and/or swallow.[87–90] Evaluation by a speech-language/swallowing therapist is needed before and after treatment to help mitigate potential problems.[91–93] Patients are also at risk for dental problems (see "Principles of Dental Evaluation and Management" in these guidelines at NCCN.org and page 886).[22] Long-term swallowing and dental dysfunction are particular risks that are worsened by multimodality therapy and require long-term specialized attention.

Oral mucositis, or tissue damage, is common in patients treated with RT for H&N cancers,[94–99] though use of advanced RT techniques (eg, intensity-modulated RT [IMRT]) may decrease the incidence and duration of this damage.[94,100] Oral mucositis causes pain in the mouth and when swallowing, which may affect the ability to eat and drink.[94,96,98,99] Oral mucositis is also associated with breaks and/or delays in treatment, as well as hospitalization.[95,97,99] Oral mucositis is worse in patients receiving concurrent systemic therapy/RT.[99] The Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology have published clinical practice guidelines for treatment of oral mucositis, though there are few high-quality studies in this area.[101] In the randomized phase III Alliance A221304 trial, patients with H&N cancer who were treated with RT (n=275) were randomized to receive a diphenhydramine-lidocaine-antacid mouthwash, doxepin mouthwash, or a placebo.[102] The reduction in mucositis pain during the first 4 hours of treatment was significantly greater in the patients who received the diphenhydramine-lidocaine-antacid mouthwash (P=.004) or the doxepin mouthwash (P=.02), compared with the placebo. Two small retrospective studies including patients with H&N cancer treated with RT or systemic therapy/RT showed that

PRINCIPLES OF SYSTEMIC THERAPY

Non-nasopharyngeal Cancer: Primary Definitive Therapy
(Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary)

- **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**
- **The preferred chemoradiotherapy approach for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy.**
- **Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (ie, sequential chemoRT). However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state-of-the-art concurrent chemoRT (cisplatin preferred, category 1) has not been established in randomized studies.**
- **Cisplatin-based induction chemotherapy followed by high-dose, every-3-week cisplatin chemoradiotherapy is associated with toxicity concerns.[1,2]**
- **After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy, including radiotherapy alone, particularly for patients with complete response after induction chemotherapy.**

Primary Systemic Therapy + Concurrent RT

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• High-dose cisplatin[3,4] (category 1) • Carboplatin/infusional 5-FU (category 1)[5,6]	• 5-FU/hydroxyurea[7] (category 2B) • Carboplatin/paclitaxel[8] (category 2B) • Cetuximab[9] (category 2B) • Cisplatin/infusional 5-FU[10] (category 2B) • Cisplatin/paclitaxel[7] (category 2B) • Weekly cisplatin 40 mg/m^2 (category 2B)[11,12]	• Select ethmoid/maxillary sinus cancers (small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features): ▸ Carboplatin/etoposide ± concurrent RT[13] ▸ Cisplatin/etoposide ± concurrent RT[13,14] ▸ Cyclophosphamide/doxorubicin/vincristine (followed by RT-based treatment) (category 2B)

Postoperative Systemic Therapy/RT

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cisplatin[15-20] (category 1 for high-risk[a] non-oropharyngeal cancers)	• None	• Docetaxel/cetuximab[21] (category 2B) (if cisplatin ineligible and positive margins and/or extranodal extension)

Induction[b]/Sequential Systemic Therapy

Preferred Regimens	Other Recommended Regimens
• Docetaxel/cisplatin/5-FU[22-25] (category 1 if induction is chosen)	• Paclitaxel/cisplatin/infusional 5-FU[26]

Systemic Therapy/RT following induction therapy, or combination chemotherapy for recurrent/persistent disease[2,27,28]

Preferred Regimens	Other Recommended Regimens
• Weekly carboplatin + concurrent RT • Weekly cisplatin (category 2B) + concurrent RT	• Weekly cetuximab + concurrent RT

Continued

[a]Adverse features: extranodal extension and/or positive margins or close margins.
[b]The categories of evidence and consensus for induction therapy vary depending on site. (See disease-specific site in the Head and Neck Table of Contents*)

*Available online, in these guidelines, at NCCN.org.

See References

treatment with gabapentin for pain from oral mucositis is associated with a reduced need for narcotic pain medication and high doses of opioids.[98,103] A single institution study demonstrated that very high-dose prophylactic gabapentin (2,700 mg daily) also reduced the number of patients requiring narcotics.[104] The toxicity of large dosages should not be underestimated and was not adequately explored in this single institution study. Larger scale studies are awaited to fully assess the generalizability and toxicity of this dosing schedule. The panel recommends consideration of doxepin, diphenhydramine-lidocaine-antacid mouthwash, or gabapentin for pain related to oral mucositis, as clinically indicated and as tolerated.

The NCCN H&N Panel Members agree that reactive feeding tube placement is appropriate in selected patients with H&N cancers.[81,85] No consensus was reached about whether prophylactic tube placement is appropriate. Advantages of prophylactic tube placement include reductions in hospitalizations and treatment-related weight loss, and improved quality of life.[105] However, this practice is also associated with disadvantages, such as longer dependence on feeding tubes and worse long-term functional outcomes, compared with a reactive approach.[105] The NCCN Guidelines provide recommendations for prophylactic tube placement, which should be strongly considered in high-risk patients (eg, those with severe pretreatment weight loss, ongoing dehydration or dysphagia, significant comorbidities, severe aspiration, anticipated swallowing issues).[81,83] In patients with adequate swallowing function, care must be given with the help of speech and language pathologists to ensure that patients continue to swallow to prevent severe fibrosis and permanent feeding tube dependence (see "Principles of Nutrition: Management and Supportive Care" in these guidelines at NCCN.org). With swallowing therapy, adequate pain control, and access to intravenous fluids, feeding tubes can be avoided in most patients. The NCCN Guidelines for H&N Cancers do not recommend prophylactic tube placement in lower-risk patients (ie, those without significant pretreatment weight loss, significant aspiration, or severe dysphagia), although these patients' weights should be carefully monitored during and after treatment.

PRINCIPLES OF SYSTEMIC THERAPY

Non-Nasopharyngeal Cancer: Recurrent, Unresectable, or Metastatic (with no surgery or RT option)

• The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary

Preferred Regimens (First-Line)

- Cetuximab/platinum (cisplatin or carboplatin)/5-FU[c,29] (category 1)
- Immunotherapy
  - Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU[c,30] (category 1)
  - Pembrolizumab (for tumors that express PD-L1 with CPS ≥1)[30,31] (category 1 if CPS ≥ 20)

Preferred Regimens (Subsequent-Line)

- Immunotherapy (if not previously used)
  - Nivolumab[32] if disease progression on or after platinum therapy (category 1)
  - Pembrolizumab[33-35] if disease progression on or after platinum therapy (category 1)

Other Recommended Regimens (First-Line)

Combination Therapy
- Cisplatin/cetuximab[36]
- Cisplatin or carboplatin/docetaxel[37] or paclitaxel[38]
- Cisplatin/5-FU[38,39]
- Cisplatin or carboplatin/docetaxel/cetuximab[40]
- Cisplatin or carboplatin/paclitaxel/cetuximab[41]

Single Agents
- Cisplatin[36,42]
- Carboplatin[43]
- Paclitaxel[44]
- Docetaxel[45,46]
- 5-FU[42]
- Methotrexate[39,47]
- Cetuximab[48]
- Capecitabine[49]

Other Recommended Regimens (Subsequent-Line)

- Combination Therapy or Single Agents
  - See preferred and other recommended first-line therapy options above
- Targeted Therapy
  - Afatinib[50] if disease progression on or after platinum therapy (category 2B)

Useful in Certain Circumstances (First- and Subsequent-Line)

- For select ethmoid/maxillary sinus cancers (small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
  - Cisplatin/etoposide or carboplatin/etoposide[14]
  - Cyclophosphamide/doxorubicin/vincristine (category 2B)

Salivary Gland Tumors

Preferred Regimens

- None

Other Recommended Regimens

- Chemotherapy (eg, cisplatin/vinorelbine, or cisplatin/doxorubicin/cyclophosphamide [category 2B])

Useful in Certain Circumstances

- Androgen receptor therapy for AR+ tumors
  - Leuprolide[51]
  - Bicalutamide[51,52]
- NTRK therapy for NTRK gene fusion-positive tumors
  - Larotrectinib[53,54]
  - Entrectinib[55,56]
- HER2 targeted therapy for HER2+ tumors (category 2B)
  - Trastuzumab[57]
- Lenvatinib (category 2B) for adenoid cystic carcinoma[58]

[c] Data suggest an overall survival advantage for patients treated with pembrolizumab/platinum/5-FU when compared to cetuximab/platinum/5-FU for first-line treatment of recurrent/metastatic head and neck squamous cell carcinoma. (Rischin D, Harrington KJ, Greil R, et al. Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). J Clin Oncol 2019:37(15_suppl): Abstract 6000.)

Continued

See References

Principles of Dental Evaluation and Management

Patients with H&N cancers are at risk for oral and dental complications after surgery or RT because of treatment-induced xerostomia and salivary gland dysfunction, which are associated with increased dental caries.[90,94,106–108] In addition, RT to the salivary and oral soft tissues is also associated with bone demineralization and trismus of the masticatory muscles. Using IMRT and limiting the RT dose to the salivary glands and oral cavity have been shown to decrease xerostomia and damage to the teeth.[106,107,109–115] Dental/oral evaluation and management can help decrease dental caries and associated problems such as dentoalveolar infection and osteoradionecrosis.[94,109,115–124]

The recommended dental/oral evaluations before, during, and after RT are described in detail in the algorithm and summarized here. A dental/oral treatment plan needs to be implemented before RT and should include the following: (1) eliminating potential sources of infection; (2) if performing dental extractions, allow adequate time for healing before RT; (3) treating active dental caries and periodontal disease; (4) treating oral candidiasis; and (5) educating patients about preventive strategies.[125] Some of the general strategies to decrease oral and dental complications include (1) decrease dry mouth (eg, by using salivary substitutes and stimulation)[126–130]; (2) reduce risk of dental caries (eg, by using topical fluoride)[116,131–134]; (3) decrease dentoalveolar infection (eg, with frequent evaluations to detect and treat disease promptly); (4) prevent and address osteoradionecrosis[135]; (5) decrease trismus of the masticatory muscles (eg, by using custom mouth-opening devices to maintain range of motion)[136–138]; and (6) have patient undergo evaluations during and after treatment to help minimize complications.[126,127,139,140] Major dental work such as extractions can be problematic for an irradiated mandible. Therefore, any planned procedures should be performed by dentists well-acquainted with this treatment setting and potential related morbidities, and in consultation with the treating radiation oncologist.

During and after treatment, the goals of dental/oral management include (1) addressing xerostomia; (2) preventing trismus; and (3) detecting and treating oral candidiasis.[125] Additional goals after treatment include (1) preventing and treating dental caries; (2) surveying

the mouth for early signs of postradiation osteonecrosis; and (3) preventing oral candidiasis.[125]

Very Advanced H&N Cancers

Very advanced H&N cancers include (1) newly diagnosed locally advanced T4b (M0); (2) newly diagnosed unresectable regional nodal disease, typically N3; (3) metastatic disease at initial presentation (M1); or (4) recurrent or persistent disease. The treatment goal is usually cure for patients with newly diagnosed locoregional but unresectable disease. For recurrent disease, the goal is cure if surgery or radiation remains feasible, or palliation if the patient has received previous RT and the disease is unresectable. For patients with widely metastatic disease, the goal is palliation or prolongation of life.

Treatment

The treatment of patients with unresectable locoregional, persistent, recurrent, or metastatic H&N cancers is dictated by the patient's performance status (PS) and intent of treatment (ie, palliative vs curative). Patients with good PS may tolerate a wide range of treatment options, whereas patients with reduced PS cannot.

Newly Diagnosed Locoregionally Advanced Disease

Many randomized trials[141–150] and meta-analyses[151–155] show significantly improved overall survival (OS), disease-free survival, and locoregional control when a systemic therapy and radiation regimen (concomitant or, less commonly, sequential) is compared with RT alone for locoregionally advanced disease. Limited data are available comparing the efficacy of different chemoradiotherapy regimens.

High-dose cisplatin plus RT is effective and typically uses conventional fractionation at 2.0 Gy per fraction to 70 Gy in 7 weeks with concurrent single-agent cisplatin given every 3 weeks at 100 mg/m^2.[141,156] Because of concerns about toxicity, a weekly lower dose cisplatin regimen (40 mg/m^2/wk) may be substituted, or other better tolerated regimens, although the categories of evidence for these regimens are lower than for high-dose cisplatin. In the absence of clearly definitive prospective comparison trials, it is unclear whether weekly cisplatin is either less toxic or equally efficacious as high-dose cisplatin.

Epidermal growth factor receptor (EGFR) overexpression is common in squamous cell H&N cancers and is associated with poor survival outcomes.[157,158] These findings have led to the development of EGFR inhibitors, such as the EGFR monoclonal antibody cetuximab. Bonner et al[159] randomly assigned 424 patients with locally advanced stage III to IV squamous cell carcinomas of the hypopharynx, oropharynx, and larynx to receive definitive RT with or without cetuximab. Locoregional control and median OS (49 vs 29.3 months; P=.03) were significantly improved in patients treated with RT and cetuximab compared with RT alone. Five-year OS in these patients was 45.6% in patients treated with RT and cetuximab and 36.4% in patients who received RT alone (hazard ratio [HR], 0.73; 95% CI, 0.56–0.95; P=.018).[160]

The addition of cetuximab to cisplatin and RT was hypothesized to improve efficacy outcomes compared with cisplatin and RT. However, the randomized phase III RTOG 0522 trial showed that the addition of cetuximab to cisplatin and RT did not significantly improve OS in patients with stage III or IV H&N cancer and, importantly, was more toxic.[161] In the phase III GORTEC 2007-01 trial, cetuximab combined with carboplatin/5-FU and RT was compared with cetuximab and RT.[162] Three-year progression-free survival (PFS) (52.3% vs 40.5%, respectively; HR, 0.73; 95% CI, 0.57–0.94; P=.015) and locoregional failure (21.6% vs 38.8%, respectively; HR, 0.54; 95% CI, 0.38–0.76; P<.001) rates were significantly better for the combination regimen, but OS and distant metastases rates were not statistically significant. Grade 3 or 4 mucositis (73% vs 61%, respectively; P=.014) and hospitalization for toxicity (42% vs 22%, respectively; P<.001) were significantly more prevalent in patients who received cetuximab combined with carboplatin/5-FU and RT. Cetuximab combined with chemoradiation continues to not be routinely used in the definitive treatment setting.

Cetuximab and RT was compared with cisplatin and RT in 2 randomized phase III trials as a deintensification treatment strategy for HPV-associated locally advanced oropharyngeal cancer, but proved inferior to cisplatin in this setting in terms of OS and was also not better tolerated.[163,164] In the RTOG 1016 noninferiority trial, 849 patients with locally advanced HPV-positive oropharyngeal cancer were randomized to receive accelerated IMRT with either cetuximab or cisplatin.[163] 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 smaller but similarly designed randomized phase III De-ESCALaTE HPV trial, cetuximab and RT was compared with cisplatin and RT in 334 patients with locally advanced p16-positive oropharyngeal squamous cell carcinoma.[164] Patients given cisplatin and 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) compared with patients given cetuximab and RT. These phase III trials demonstrate that cetuximab and RT is inferior to cisplatin and RT in patients with HPV-related oropharyngeal cancer.[163,164]

Therefore, in patients with a PS of 0 or 1, the recommended treatment of newly diagnosed, very advanced disease is concurrent systemic therapy/RT, with a large amount of phase III data supporting high-dose cisplatin as a category 1 preferred recommendation.[141,165] There is also considerable phase III data from Europe that supports the use of carboplatin/5-FU with concurrent RT.[166] This treatment is also considered a category 1 preferred option. Cisplatin-based induction systemic therapy can be used, followed by radiation-based locoregional treatment (ie, sequential chemoradiation). However, an improvement in OS with the incorporation of induction chemotherapy, compared with proceeding directly to state-of-the-art concurrent systemic therapy/RT has not been established in randomized studies.[167,168] Cetuximab with concurrent RT is a category 2B option based on phase II and phase III data but is distinctly inferior to cisplatin with concurrent RT, as discussed previously.[160,163,164,169] Other chemoradiation options that are also category 2B based on less panel consensus include 5-FU/hydroxyurea, cisplatin with infusional 5-FU, platinum combined with paclitaxel, and weekly cisplatin 40 mg/m^2.[170–174] Other options for patients with a PS of 2–3 are described in the algorithm (see "Treatment of Newly Diagnosed (M0) T4b, N0-3 or Unresectable Nodal Disease or Unfit for Surgery," page 874). Primary systemic therapy/RT regimens are listed in the "Principles of Systemic Therapy" in the algorithm (see "Principles of Systemic Therapy for Non-Nasopharyngeal Cancer: Primary Definitive Therapy," page 885). Radiation therapy fractionation for patients with newly diagnosed, very advanced disease is described in the "Principles of Radiation Therapy" in the NCCN Guidelines at NCCN.org.

Metastatic Disease

For patients with metastatic (M1) disease at initial presentation, palliative adjunctive measures include analgesics and other measures to control manifestations of disease spread (eg, pain, hypercalcemia, malnutrition). Locoregional treatment (eg, surgery, RT, or ablative therapies) may be used for oligometastatic disease.[175–177]

Single agent and combination systemic therapy are both used (see "Treatment of Metastatic Disease at Initial Presentation" and "Principles of Systemic Therapy for Non-Nasopharyngeal Cancer: Recurrent, Unresectable, or Metastatic," pages 875 and 886).[178] Response rates to single-agent therapies range from 15% to 35%.[179–181] Randomized trials assessing a cisplatin-based combination regimen (cisplatin/5-FU) versus single-agent therapy with cisplatin, 5-FU, or methotrexate showed significantly higher response rates, but no difference in OS and greater toxicity for the combination regimen.[182–186] Complete response is associated with longer survival and, although infrequent, has been reported more often with combination regimens.[183] A phase III randomized trial (EXTREME) of 442 patients found that cetuximab plus cisplatin/5-FU or carboplatin/5-FU improved median survival compared with the standard chemotherapy doublet of platinum/5-FU (10.1 vs 7.4 months; P=.04).[187] The response rate was improved with the addition of cetuximab (36% vs 20%; P<.001). A randomized phase III trial found no significant difference in survival when comparing cisplatin/5-FU and cisplatin/paclitaxel.[182]

Trials evaluating immune checkpoint inhibitors demonstrated efficacy in patients with recurrent or metastatic HNSCC.[188–190] Pembrolizumab, an anti-PD-1 antibody, was evaluated as a first-line option for recurrent or metastatic HNSCC in the KEYNOTE-048 trial (n=882).[188] Patients were randomized to receive pembrolizumab, pembrolizumab with a platinum and 5-FU, or the EXTREME regimen. In the total population, an OS benefit was observed in the pembrolizumab with a platinum and 5-FU arm, compared with the EXTREME arm (median OS, 13 vs 10.7 months, respectively; HR, 0.77; 95% CI, 0.63–0.93; P=.003). PFS, however, did not significantly differ between these 2 study arms. In patients with a PD-L1 combined positive score (CPS) of both ≥20 and ≥1, median OS was better in patients who received pembrolizumab monotherapy, compared with those who received the EXTREME regimen (median 14.9 vs 10.7 months, respectively; HR, 0.61; 95% CI, 0.45–0.83; P<.001, for CPS ≥20; median 12.3 vs 10.3 months, respectively; HR, 0.78; 95% CI, 0.64–0.96; P=.009, for CPS ≥1). Median duration of response was greater in patients treated with pembrolizumab monotherapy or pembrolizumab with chemotherapy, compared with patients treated with the EXTREME regimen.

Based on the results of KEYNOTE-048,[188] the panel considers pembrolizumab/platinum/5-FU a preferred first-line option (category 1) for all patients with recurrent, unresectable, or metastatic disease who have no surgical or radiotherapeutic option. The panel also considers pembrolizumab monotherapy as a preferred first-line option for patients with CPS ≥1 (category 1 if CPS ≥20). Other combination regimens recommended by the panel for treatment of metastatic HNSCC include (1) cisplatin or carboplatin, plus 5-FU with cetuximab (category 1; preferred)[187]; (2) cisplatin or carboplatin, plus a taxane[182,191]; (3) cisplatin with cetuximab[192,193]; (4) cisplatin with 5-FU[182,183]; or (5) cetuximab with a platinum and a taxane.[193–196] Single agents recommended by the panel include cisplatin, carboplatin,

paclitaxel, docetaxel, 5-FU, methotrexate, capecitabine, and cetuximab.[178,181,183,184,192,197–205]

Recurrent or Persistent Disease

Surgery is recommended for resectable recurrent or persistent locoregional disease, in the absence of distant metastatic disease; adjuvant therapy depends on the risk factors (see "Recurrent or persistent disease," page 874). Patients with resectable recurrent or persistent locoregional disease who have not previously been treated with RT may also be treated with concurrent systemic therapy/RT (high-dose cisplatin is the preferred [category 1] systemic agent).[141] Combination systemic therapy followed by RT or systemic therapy/RT is a category 3 recommendation for these patients. If the recurrence is unresectable and the patient had not had prior RT, then RT with concurrent systemic therapy is recommended, depending on the PS (see "Recurrent or persistent disease," page 874). For patients with recurrent disease who are not amenable to curative-intent radiation or surgery, the treatment approach is the same as that for patients with metastatic disease. Locoregional treatment may be considered in the presence of distant metastasis with locoregional failure. RT fractionation for patients with recurrent or persistent disease is described in the "Principles of Radiation Therapy" in these guidelines online (available at NCCN.org).

Disease That Has Progressed on or After Platinum Therapy

For failure of platinum-based therapy, options are listed in the algorithm (see "Principles of Systemic Therapy for Non-Nasopharyngeal Cancer: Recurrent, Unresectable, or Metastatic," page 886).

Nivolumab was assessed in a phase III randomized clinical trial including 361 patients with recurrent HNSCC whose disease had progressed within 6 months after platinum-based chemotherapy.[190] With a median follow-up of 5.1 (range, 0–16.8) months, the OS was significantly greater in patients given nivolumab compared with patients given standard second-line single-agent systemic therapy (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, relative to patients who received standard therapy (36.0% vs 16.6%, respectively), and response rate was higher (13.3% vs 5.8%, respectively), but median PFS was not significantly different between the 2 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 patients with a tumor PD-L1 expression level of 1% or more (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 shown for the nivolumab-treated patients (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 patients who received standard therapy. These results indicate that nivolumab prolongs survival in patients with recurrent or metastatic HNSCC cancer that has progressed after platinum-based chemotherapy, relative to patients who receive standard single-agent systemic therapy.

Pembrolizumab was initially studied at a dose of 10 mg/kg given every 2 weeks in the HNSCC cohort of the KEYNOTE-012 trial, and clinical activity was identified.[206] A lower, fixed-dose schedule using pembrolizumab 200 mg every 3 weeks was subsequently assessed in a phase 1b expansion cohort of 132 patients with recurrent or metastatic HNSCC.[207] At 6 months, the OS rate was 59%, and the PFS was 23%, with an overall response rate of 18%. Observed responses appeared durable although the follow-up was limited (median 9 months). Pembrolizumab was also generally well-tolerated.[206] Pooled analyses after long-term follow-up of the initial and expansion cohorts (n=192) showed a 1-year OS rate of 38%.[208] Among the 34 patients who showed a response, 85% of the responses lasted 6 months or longer, and 71% lasted 12 months or longer.

Based on results of the phase Ib KEYNOTE-012 trial, pembrolizumab was evaluated in the phase III KEYNOTE-040 trial.[189] Patients with recurrent or metastatic HNSCC (n=495) were randomized to receive pembrolizumab or another systemic therapy (methotrexate, docetaxel, or cetuximab). Median OS was greater for the pembrolizumab arm compared with the standard-of-care arm (8.4 vs 6.9 months; HR, 0.80; 95% CI, 0.65–0.98; P=.016). When analyses were stratified by PD-L1-status, the results for OS were significantly better with pembrolizumab only for patients with tumors that have PD-L1 expression.

The nonrandomized phase II KEYNOTE-055 trial studied pembrolizumab in 171 patients with HNSCC that progressed after treatment with both a platinum and cetuximab.[209] The overall response rate was 16% (95% CI, 11%–23%), and the mean duration of response was 8 months.

Afatinib was evaluated in the phase III LUX-Head & Neck 1 RCT. Afatinib was compared with methotrexate in patients with recurrent or metastatic H&N cancer who had progressed on or after platinum-based therapy (n=483).[210] Patients randomized to receive afatinib had greater PFS compared with patients randomized to receive methotrexate (2.6 vs 1.7 months; P=.03). There were no significant differences for OS.[210] The PFS benefit with afatinib seemed to be most clear in the HPV-negative group.[211] A randomized phase II trial comparing afatinib

to cetuximab in patients with recurrent or metastatic H&N cancer who had progressed on or after platinum-based therapy (n=121) showed comparable response rates between the 2 drugs.[212]

The panel recommends immunotherapy (nivolumab and pembrolizumab) as category 1 preferred options for patients with recurrent or metastatic HNSCC who have progressed on or after platinum-based chemotherapy based on high-quality evidence.[189,190] 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 HNSCC (ie, greater likelihood of response to pembrolizumab and greater survival benefit in response to nivolumab). For all other systemic therapy options recommended by the panel, there are no clear advantages of one agent over another in the subsequent line setting, though response rates seem to be highest with taxanes. Afatinib has a PFS benefit, but not an OS benefit, over methotrexate[210] and is a category 2B systemic therapy option for non-nasopharyngeal persistent H&N cancer or cancer that has progressed on or after platinum-containing chemotherapy.

Salivary Gland Tumors

Guidelines recommendations regarding treatment of salivary gland tumors have recently been considerably revised, notably systemic therapy recommendations. Salivary gland tumors can arise in the major salivary glands (ie, parotid, submandibular, sublingual) or in one of the minor salivary glands, which are widely spread throughout the aerodigestive tract.[213] Many minor salivary gland tumors are located on the hard palate. Approximately 20% of the parotid gland tumors are malignant; the incidence of malignancy in submandibular and minor salivary gland tumors is approximately 50% and 80%, respectively. These malignant tumors constitute a broad spectrum of histologic types, including mucoepidermoid, acinic, adenocarcinoma, adenoid cystic carcinoma, malignant myoepithelial tumors, and squamous cell carcinoma. The primary diagnosis of squamous cell carcinoma of the parotid gland is rare; however, the parotid gland is a frequent site of metastasis from skin cancer.[214] Prognosis and tendency to metastasize vary among these histologic types. Major prognostic factors are histologic grade, tumor size, and local invasion. Staging is done using the AJCC Cancer Staging Manual (8th edition).[14]

Treatment

The major therapeutic approach for salivary gland tumors is adequate and appropriate surgical resection (see "Salivary Gland Tumors: Clinically Benign or T1, T2; T3, T4a; T4b," page 879).[215–218] Surgical intervention requires careful planning and execution, particularly in parotid tumor surgery, because the facial nerve is in the gland. The gland should be preserved if the nerve is not directly involved by the tumor. Most parotid gland tumors are located in the superficial lobe. If the facial nerve is functioning preoperatively, the nerve can be preserved in most patients.[219] The facial nerve should be killed if there is preoperative facial nerve involvement with facial palsy or if there is direct invasion of the tumor into the nerve where the tumor cannot be separated from the nerve. Malignant deep lobe parotid tumors are quite rare; however, they are generally a challenge for the surgeon because the patient may require superficial parotidectomy and identification and retraction of the facial nerve to remove the deep lobe parotid tumor.

The panel recommends highly conformal RT techniques such as IMRT, proton, or other heavy ions for definitive radiation treatment (see "Salivary Gland Tumors: Principles of Radiation Therapy," page 882). Results from a retrospective cohort study including 545 patients with salivary gland tumors treated between 1997 and 2010 showed better local control and survival outcomes with neutron therapy, relative to photon therapy.[220] However, risk of late effects with neutron therapy is high and tends to increase over time, with estimates as high as 20% at 9 years.[221,222] The panel no longer recommends neutron therapy as a general solution for salivary gland cancers due to the diminishing demand, concerns regarding the methodologic robustness of available randomized trial data, and closure of all but one center in the United States. The panel recognizes the potential clinical value of neutron therapy for select patients.

Most malignant deep lobe parotid tumors will require postoperative RT because of adverse features such as the limitations of surgical margins in the resection of these tumors.[215,217,223] RT is also used in an adjuvant setting for tumors with other adverse features (eg, intermediate, high grade, T3–4 tumors, or positive lymph nodes)[216,224,225]; systemic therapy/RT (category 2B) can also be considered.[226] Efficacy data for systemic therapy/RT for patients with advanced salivary gland tumors that have been resected are limited. Extensive safety data are available and may be extrapolated from the management of HNSCC, with some NCCN Member Institutions using platinum-based regimens for these patients. With regard to unresectable salivary gland tumors, the NCCN H&N Panel had less consensus about chemoradiation (which is reflected in the category 2B recommendations), because there are few published trials. Clinical trials are ongoing in this area (eg, ClinicalTrials.gov identifiers: NCT01220583, NCT02776163).

Systemic therapy may be used for palliation in advanced disease (see algorithm pages "Salivary Gland Tumors: Treatment for Recurrence," page 881 and "Principles of Systemic Therapy: Salivary Gland Tumors," page 886). Targeted therapy is increasingly becoming an

option for patients with distantly metastatic salivary gland tumors. A significant number of advanced salivary gland tumors with distant metastases are androgen receptor–positive.[227–231] Therefore, the panel recommends that patients with tumors that are androgen receptor–positive receive androgen receptor therapy (eg, leuprolide, bicalutamide).[231–234] Two phase I–II studies including patients with advanced *NTRK* gene fusion-positive cancer (with 22%–38% being salivary gland tumors) showed promising objective response rates of 75%–100% with the tyrosine receptor kinase (TRK) inhibitor larotrectinib.[235,236] A pooled analysis from a phase II trial and 2 phase I trials including 54 patients with *NTRK* gene fusion-positive cancer (13% being mammary analog secretory carcinoma of the salivary gland) showed an objective response rate of 57.4% for entrectinib, another TRK inhibitor.[237] The FDA recently approved larotrectinib and entrectinib for treatment of patients with *NTRK* gene fusion-positive tumors, and the panel also recommends NTRK therapy options such as larotrectinib and entrectinib for patients with recurrent *NTRK* gene fusion-positive salivary gland tumors and distant metastases.

Finally, HER2 positivity has also been found in some advanced salivary gland tumors.[229,231,238] It is recommended that these patients receive a HER2-targeted treatment option such as trastuzumab,[231,239,240] but this is a category 2B recommendation based on less consensus among the panel. Small series demonstrate that ado-trastuzumab emtansine may be active in patients with previously treated metastatic HER2-positive salivary gland cancers.[241,242] AR and HER2 status should be checked in patients with distant metastases. *NTRK* status should be evaluated in mammary analog secretory carcinoma of the salivary gland.[243] Various combinations of chemotherapy agents (eg, cisplatin/cyclophosphamide/doxorubicin and cisplatin/vinorelbine) have been shown in small series to be active for some salivary gland malignant histologies, with overall response rates ranging from 27% to 60%,[244–246] and chemotherapy regimens such as these are acknowledged by the NCCN Guidelines Panel as treatment options for patients with advanced disease (category 2B). A phase II trial including 32 patients with recurrent or metastatic adenoid cystic carcinoma showed a disease control rate of 88% (partial response of 15.6%, stable disease in 75%) for lenvatinib.[247] Based on these results and lack of other evidence-based options for recurrent or metastatic adenoid cystic carcinoma, lenvatinib is a category 2B option. Use of other tyrosine kinase inhibitors such as axitinib,[248] sorafenib,[249] sunitinib,[250] and dovitinib[251] have been evaluated in phase II trials for salivary gland tumors, but larger trials are needed in this area.

Summary

Much progress has been made in understanding the epidemiology, pathogenesis, and management of H&N cancers. Treatment planning for H&N cancers involves a multidisciplinary team of healthcare professionals with expertise in H&N surgery, radiation oncology, medical oncology, plastic and reconstructive surgery, dentistry, speech and swallowing therapy, nutrition, pathology, and diagnostic/interventional radiology, among others. Care should be taken in selection of appropriate imaging studies for patients with H&N cancers. Dental management for prevention and treatment of RT effects should be provided, as well as adequate nutritional support to prevent severe weight loss. Recent phase III RCTs support the use of immunotherapy for patients with recurrent, unresectable, or metastatic H&N cancer. Immunotherapy options for patients with recurrent or metastatic HNSCC who have progressed on or after platinum-based chemotherapy include nivolumab and pembrolizumab. Pembrolizumab is also a first-line option when administered in combination with platinum/5-FU or as a monotherapy in patients with CPS ≥1 (category 1 if CPS ≥20). The panel has recently expanded the list of systemic therapy options for patients with salivary gland tumors (eg, larotrectinib and entrectinib for patients with recurrent *NTRK* gene fusion-positive salivary gland tumors and distant metastases).

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