NCCN Guidelines® Insights

Head and Neck Cancers, Version 1.2018

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Head and Neck (H&N) Cancers provide treatment recommendations for cancers of the lip, oral cavity, pharynx, larynx, ethmoid and maxillary sinuses, and salivary glands. Recommendations are also provided for occult primary of the H&N, and separate algorithms have been developed by the panel for very advanced H&N cancers. These NCCN Guidelines Insights summarize the panel's discussion and most recent recommendations regarding evaluation and treatment of nasopharyngeal carcinoma.

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to 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 NCCN Guideline Panel discussion, including the literature reviewed.**

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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

The NCCN staff listed below discloses no relevant financial relationships:
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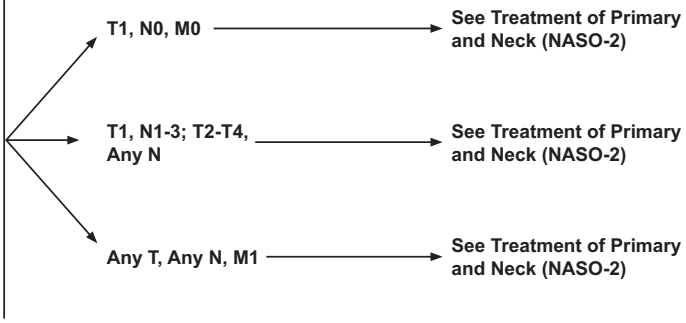
WORKUP

- **H&P[a,b] including a complete head and neck exam; mirror examination as clinically indicated**
- **Nasopharyngeal fiberoptic examination**
- **Biopsy of primary site or FNA of the neck**
- **MRI with contrast of skull base to clavicle ± CT of skull base/neck with contrast as clinically indicated to evaluate skull base erosion**
- **Dental,[c] nutritional, speech and swallowing, and audiology evaluations as clinically indicated[d]**
- **Imaging for distant metastases with FDG-PET/CT and/or chest CT with contrast**
- **Consider Epstein-Barr virus (EBV)/DNA testing[e]**
- **Consider ophthalmologic and endocrine evaluation as clinically indicated.**

Multidisciplinary consultation as clinically indicated

CLINICAL STAGING



[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. Smoking cessation counseling as clinically indicated. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depression (See NCCN Guidelines for Distress Management).
[c]See Principles of Dental Evaluation and Management (DENT-A).
[d]See Principles of Nutrition: Management and Supportive Care (NUTR-A).
[e]For nonkeratinizing or undifferentiated histology, consider testing for EBV in tumor and blood. Common means for detecting EBV in pathologic specimens include in situ hybridization for EBV-encoded RNA (EBER) or immunohistochemical staining for latent membrane protein (LMP). The EBV DNA load within the serum or plasma may be quantified using polymerase chain reaction (PCR) targeting genomic sequences of the EBV DNA such as BamHI-W, EBNA, or LMP; these tests vary in their sensitivity. The EBV DNA load may reflect prognosis and change in response to therapy.

NASO-1

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

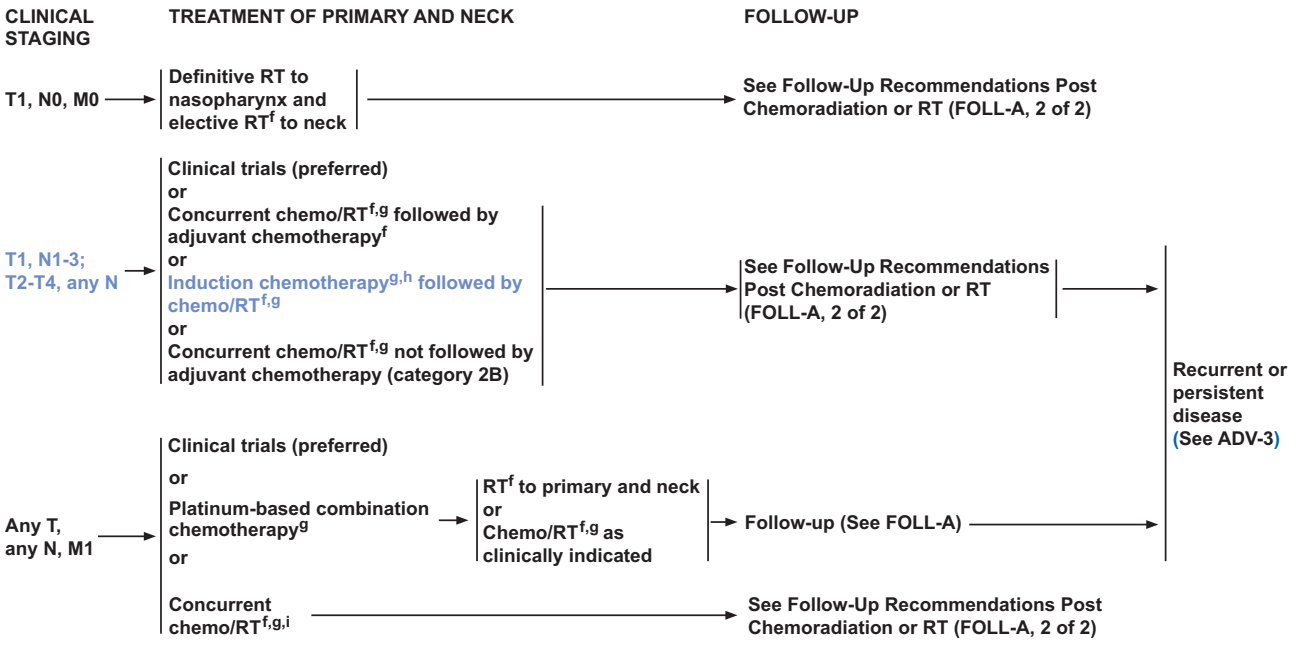
Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Nasopharyngeal carcinoma (NPC) is a rare cancer, accounting for 0.6% of all cancers diagnosed worldwide in 2012.[1] However, there are areas of the world with endemic disease; global incidence rates are highest in Southeast Asia (especially southern China), Micronesia/Polynesia, Eastern Asia, and North Africa.[1,2] Rates are 2 to 3 times higher in men than in women.[1,2] Among head and neck (H&N) cancers, NPC has one of the highest propensities to metastasize to distant sites. Regional recurrences are uncommon, occurring in only 10% to 19% of patients.[3,4] The NCCN Guidelines for the evaluation and management of NPC provide recommendations aimed at addressing the risks for local, regional, and distant disease.

Workup for NPC

The workup of NPC (see NASO-1, above) includes a complete H&N examination, nasopharyngeal en-



[f]See Principles of Radiation Therapy (NASO-A).
[g]See Principles of Systemic Therapy (CHEM-A).
[h]See Discussion on induction chemotherapy.
[i]Can be used for select patients with distant metastasis in limited site or with small tumor burden, or for patients with symptoms in the primary or any nodal site.

NASO-2

doscopic examination, biopsy, and MRI encompassing the skull base, face, and entire neck with or without CT as needed for evaluation of bone invasion at the skull base. FDG-PET/CT and/or chest CT may be used to evaluate for distant metastases, especially for locoregionally advanced disease (when the incidence of metastasis at diagnosis is significant); if only a chest CT is ordered, a bone scan for distant bone metastasis is needed. These studies are important to determine the full extent of tumor in order to assign the stage, determine the appropriateness and choice of systemic therapy agents, and, if the disease remains limited to the H&N, to design radiation volumes that will encompass all the disease with appropriate doses. Epstein-Barr virus (EBV) DNA testing may also be considered (see "Epstein-Barr Virus," following section). Multidisciplinary consultation is encouraged. Dental, nutritional, speech and swallowing, and audiology evaluations should be performed as clinically indicated. Ophthalmologic and endocrinologic assessments may also be considered.

Human papillomavirus (HPV) infection has been found to be associated with WHO type I NPC in case reports and very small case series, but the limited data regarding the impact on chemoradiation (CRT) outcomes are conflicting.[5–7] Therefore, routine testing for HPV in NPC is not recommended by the NCCN H&N Panel.

Epstein-Barr Virus

Infection with EBV is an etiologic factor in the development of NPC.[8,9] Workup for NPC may include EBV testing of both the tumor itself and the blood, particularly in the presence of nonkeratinizing and undifferentiated histology.[10–12] Testing methods for detection of EBV in the tumor include in situ hybridization for EBV-encoded RNA[13] and immunohistochemical staining for LMP1.[14] The former tends to be a more sensitive testing method for carcinomas, relative to LMP1 immunohistochemical staining.[15] PCR may be used to evaluate EBV DNA load in plasma. Sensitivity and specificity values range

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PRINCIPLES OF RADIATION THERAPY[1]

DEFINITIVE:
RT Alone (for T1, N0 or patients who are not eligible to receive chemotherapy)
- **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))**
    - **66 Gy (2.2 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[2,3]**
    - **69.96 Gy (2.12 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]**

CONCURRENT CHEMORADIATION:[6]
(preferred for patients eligible for chemotherapy)
- **PTV**
  - **High risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks[2]**
  - **Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[5]**

Either IMRT (preferred) or 3D conformal RT is recommended for cancers of the nasopharynx to minimize dose to critical structures. 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]Care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
[3]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.
[4]Lee NY, Zhang Q, Pfister DG, et al. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. Lancet Oncol 2012;13:172-180.
[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).
[6]See Principles of Systemic Therapy (CHEM-A).

NASO-A

from 53% to 96% and 88% to 100%, respectively.[16] Testing for plasma EBV DNA has been used in select centers as a means of residual disease monitoring. For patients with locoregional disease, studies have shown that high initial levels of plasma EBV DNA, or persistently elevated levels near or at the end of radiation therapy (RT), are associated with a significantly poorer outcome following RT or CRT.[17–22] A meta-analysis including 13 studies showed that plasma EBV DNA levels assessed pretreatment were associated with mortality (hazard ratio [HR], 2.81; 95% CI, 2.44–3.24; *P*<.001) and distant metastasis (HR, 3.89; 95% CI, 3.39–4.47; *P*<.001), although these studies were significantly heterogeneous (*P*=.03).[23] Plasma EBV DNA has also been studied as an indicator of disease response to chemotherapy as induction therapy prior to CRT[24] and in the setting of distant metastases.[25]

Treatment of NPC

Locoregionally Advanced Disease

The Intergroup 0099 trial, which randomly assigned patients to external-beam RT plus chemotherapy versus external-beam RT alone, closed early when an interim analysis disclosed a significant survival advantage favoring the combined chemotherapy and RT group.[26] The addition of chemotherapy also decreased local, regional, and distant recurrence rates. Subsequent phase III randomized trials in Asia confirmed that concurrent CRT increased survival compared with RT alone.[27–29] In one of these trials, the 5-year overall survival (OS) rate was 70% for the CRT group versus 59% for the RT group.[27] The randomized study conducted in Singapore, which was modeled after the Intergroup 0099 treatment regimen, continued to show the benefit of adding chemotherapy to RT. After combined cisplatin and RT, adjuvant cisplatin/5-FU was also given.[29] This regimen appeared to reduce toxicity while still providing a beneficial antitumor effect. However, a phase III

PRINCIPLES OF SYSTEMIC THERAPY

The choice of systemic therapy should be individualized based on patient characteristics (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 not recommended due to toxicity concerns.[1,2]**
- **After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone versus radiotherapy plus weekly carboplatin or cetuximab are among the options.**

Squamous Cell Cancers

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

- **Primary systemic therapy + concurrent RT**
  - **High-dose cisplatin[3,4] (preferred) (category 1)**
  - **Cetuximab[5] (category 1 for oropharynx, hypopharynx, or larynx; category 2B for lip, oral cavity, ethmoid sinus, maxillary sinus, occult primary)**
  - **Carboplatin/infusional 5-FU (category 1)[6,7]**
  - **5-FU/hydroxyurea[8]**
  - **Cisplatin/paclitaxel[8]**
  - **Cisplatin/infusional 5-FU[9]**
  - **Carboplatin/paclitaxel[10] (category 2B)**
  - **Weekly cisplatin 40 mg/m^2 (category 2B)[11,12]**
- **Postoperative chemoradiation**
  - **Cisplatin[13-18] (category 1 for high-risk** non-oropharyngeal cancers)**

Nasopharynx:

- **Chemoradiation followed by adjuvant chemotherapy**
  - **Cisplatin + RT followed by cisplatin/5-FU[19-20] or carboplatin/5-FU[21] (category 2B for carboplatin/5-FU)**
- **Cisplatin + RT without adjuvant chemotherapy (category 2B)[22]**

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

- **Induction*/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[23-25] (category 1 if induction is chosen)**
  - **Paclitaxel/cisplatin/infusional 5-FU[26]**
  - **Following induction, agents used with concurrent chemoradiation typically include weekly carboplatin, weekly cisplatin (category 2B), or weekly cetuximab[1,27,28]**

Nasopharynx:

- **Induction/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[29]**
  - **Docetaxel/cisplatin (category 2B)[30]**
  - **Cisplatin/5-FU[24]**
  - **Cisplatin/epirubicin/paclitaxel**
  - **Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[20] or carboplatin[27]**

See references on CHEM-A 3–5 (available at NCCN.org)

*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)

**Adverse features: extranodal extension and/or positive margins.

Continued

randomized trial from China comparing concurrent cisplatin/RT with (or without) adjuvant cisplatin/5-FU showed that adjuvant chemotherapy did not significantly improve survival following CRT (HR, 0.74; 95% CI, 0.49–1.10; *P*=.13).[30]

An individual patient data meta-analysis by Blanchard et al,[31] which included 19 trials and 4,806 patients with nonmetastatic NPC, showed that both adjuvant chemotherapy following CRT and CRT without adjuvant chemotherapy were associated with better OS (HR, 0.65; 95% CI, 0.56–0.76, and HR, 0.80; 95% CI, 0.70–0.93, respectively) and progression-free survival (PFS; HR, 0.62; 95% CI, 0.53–0.72, and HR, 0.81; 95% CI, 0.71–0.92, respectively). However, differences between the included studies assessing CRT with and without adjuvant chemotherapy (eg, different length of follow-up, fewer patients with stage II disease in trials assessing adjuvant chemotherapy) limited the ability to make a firm conclusion regarding the efficacy of one treatment modality over the other. A network meta-analysis based on this individual patient data meta-analysis[31] (including 20 trials and 5,144 patients) showed that the addition of adjuvant chemotherapy to CRT was associated with better PFS (HR, 0.81; 95% CI, 0.66–0.98) compared with CRT only.[32] The authors argued that more chemotherapy, in addition to concurrent CRT, could reduce recurrence rates. The NRG-HN001 trial (ClinicalTrials.gov identifier: NCT02135042) is currently in progress to further investigate the role of adjuvant chemotherapy following CRT in patients with locoregionally advanced NPC; in part, delivery of adjuvant chemotherapy is individualized based on EBV DNA plasma levels.

Induction chemotherapy (prior to concurrent CRT) is also a treatment option for patients with locoregionally advanced NPC. In a recent phase III randomized multi-institutional trial from China including 480 patients with stage III–IVb N-positive disease, those randomized to receive induction cisplatin/5-FU/docetaxel (TPF) with concurrent

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PRINCIPLES OF SYSTEMIC THERAPY

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

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

- **First-Line Combination Therapy Options:**
  - **Cisplatin or carboplatin/5-FU/cetuximab[30] (non-nasopharyngeal) (category 1)**
  - **Cisplatin or carboplatin/docetaxel[31] or paclitaxel[32]**
  - **Cisplatin/cetuximab[33] (non-nasopharyngeal)**
  - **Cisplatin/5-FU[32,34]**
  - **Cisplatin or carboplatin/docetaxel/cetuximab[35] (non-nasopharyngeal)**
  - **Cisplatin or carboplatin/paclitaxel/cetuximab[36,37] (non-nasopharyngeal)**
  - **Cisplatin/gemcitabine[39,40] (category 1) (nasopharyngeal)**
  - **Carboplatin/cetuximab[41] (nasopharyngeal)**
- **First-Line Single-Agent Options:**
  - **Cisplatin[33,42]**
  - **Carboplatin[43]**
  - **Paclitaxel[44]**
  - **Docetaxel[45,46]**
  - **5-FU[42]**
  - **Methotrexate[47,48]**
  - **Cetuximab[49] (non-nasopharyngeal)**
  - **Gemcitabine[50] (nasopharyngeal)**
  - **Capecitabine[51]**
- **Second-Line Therapy or Subsequent Therapy Options:**
  - **Combination therapy options listed above**
  - **Single-agent options listed above**
  - **Nivolumab[52] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 1)**
  - **Pembrolizumab[53-55]**
    - **Non-nasopharyngeal: if disease progression on or after platinum-containing chemotherapy**
    - **Nasopharyngeal: if previously treated, PD-L1-positive recurrent or metastatic disease (category 2B)**
  - **Afatinib[56] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 2B)**

See references on CHEM-A 3–5 (available at NCCN.org)

CHEM-A 2 OF 5

CRT had a better 3-year failure-free survival rate (80%; 95% CI, 75–85) compared with patients who received solely CRT (72%; 95% CI, 66–78, and HR, 0.68; 95% CI, 0.48–0.97; *P*=.034).[33] Grade 4 adverse events occurred in 18% of patients who received induction TPF with concurrent RT compared with 1% who received CRT only (*P*<.001), with neutropenia (15%) and leucopenia (5%) the most common grade 4 adverse events in the induction chemotherapy group. In another randomized trial from China, patients with stage III–IVb NPC who received induction cisplatin/5-FU followed by CRT (n=238) had a better 3-year disease-free survival rate (82%; 95% CI, 0.77–0.87) compared with patients (n=238) who received CRT only (74%; 95% CI, 0.68–0.80; *P*=.028).[34] Multivariate analyses showed a significant difference between treatment arms for disease-free survival (HR, 0.67; 95% CI, 0.47–0.95; *P*=.023) and distant metastasis-free survival (HR, 0.63; 95% CI, 0.41–0.98; *P*=.038). However, OS was not significantly better in patients receiving the induction chemotherapy regimen. Finally, in a complex randomized trial (including one substudy comparing induction chemotherapy with adjuvant chemotherapy administration, given either before or after definitive CRT), unadjusted comparisons of induction versus adjuvant chemotherapy did not reach statistical significance, but select adjusted comparisons indicated some improvements in disease progression or death associated with assignment to induction.[35]

Taken together, results thus far suggest that induction chemotherapy prior to CRT in patients with locally advanced NPC may potentially impact tumor control, compared with CRT without additional chemotherapy.[32,36] Expert groups (eg, ESMO, NCI) differ in their clinical practice guidelines regarding use of induction chemotherapy for these patients,[37] and the NCCN Guidelines Panel could not reach uniform consensus in this regard. Clinical trials are currently ongoing to address the role of induction chemotherapy prior to CRT for patients with locoregionally advanced NPC (eg, ClinicalTrials.gov iden-

tifiers: NCT01872962, NCT02512315). Currently available evidence shows trends favoring the addition of chemotherapy to concurrent CRT in patients with locoregionally advanced NPC[32]; however, it is unclear whether to administer chemotherapy before or after CRT for these patients.

NCCN Recommendations: Patients with T1,N0,M0 nasopharyngeal tumors should be treated with definitive RT alone, including elective RT to the neck (see NASO-2, page 482). For patients with locoregionally advanced NPC (T1,N1–3; T2–T4,any N), enrollment in a clinical trial is preferred. The panel recommends concurrent CRT (cisplatin) with adjuvant chemotherapy (cisplatin/5-FU) for locoregionally advanced NPC. Concurrent CRT (cisplatin) without adjuvant systemic therapy is a category 2B recommendation based on a single randomized trial from China, which did not demonstrate a clear superiority over delivery of adjuvant chemotherapy.[30] Cisplatin for CRT is recommended for patients with no contraindication to the drug, because most randomized trials support the use of cisplatin in this setting (see CHEM-A 1 of 5, page 484).[26,27] If using adjuvant chemotherapy, adjuvant carboplatin/5-FU is a widely accepted option; however, this recommendation is a category 2B option due to the uncertainty about the benefits of adjuvant chemotherapy for all patients with NPC.[38]

Induction chemotherapy (followed by CRT) is also recommended for patients with NPC with either T1,N1–3 or T2–T4,any N lesions (see NASO-2, page 482). Based on the results from randomized trials[33–35] and a meta-analysis,[32] the panel voted to change the category recommendation for induction chemotherapy followed by CRT from category 3 to category 2A for the 2018 update. Besides TPF, several other induction/sequential chemotherapy regimens are recommended in the algorithm for NPC[27,39–41] (see CHEM-A 1 of 5, page 484).

Metastatic Disease

For patients with NPC who present with metastatic (M1) disease, enrollment in a clinical trial is preferred. Other recommended initial therapy options include either a platinum-based combination systemic therapy regimen or CRT; treatment depends on whether disease is mostly localized or widespread and if it is symptomatic or posing a clinical risk to the patient.[26,27,38] Patients who receive chemotherapy alone may receive subsequent RT to the primary and neck or concurrent CRT as clinically indicated. Population-based data appear to support the role of earlier RT in the management of metastatic disease.[42]

Active combination regimens for these patients include gemcitabine/cisplatin (category 1)[43,44]; cisplatin or carboplatin, plus a taxane[45,46]; cisplatin/5-FU[46,47]; or carboplatin/cetuximab.[48] Results from a trial that compared 5 different cisplatin-based regimens for NPC showed that a gemcitabine/cisplatin regimen was effective, although not better than either cisplatin/5-FU or cisplatin/paclitaxel.[49] However, results from a recent randomized phase III trial showed that patients with recurrent or metastatic NPC (N=362) who received gemcitabine/cisplatin had a greater median PFS compared with those who received cisplatin/5-FU (7.0 vs 5.6 months, respectively; HR, 0.55; 95% CI, 0.44–0.68; $P<.001$).[44] Gemcitabine/vinorelbine was removed from the list of recommendations for the 2018 update because there are more data to support use of other regimens. Active and more commonly used single agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, capecitabine, and gemcitabine.[47,50–61]

In 2016, the anti–PD-1 antibody pembrolizumab received FDA approval for use in patients with recurrent or metastatic squamous cell H&N cancer who have progressed on or following platinum-based chemotherapy. The panel subsequently added pembrolizumab to the NCCN Guidelines for this indication, excluding NPC. Pembrolizumab in patients with PD-L1–positive recurrent or metastatic NPC was assessed in the nonrandomized, multi-institutional, phase IB KEYNOTE-028 trial (N=27).[62] All but 2 of the patients had previously received systemic therapy for recurrent or metastatic disease. The objective response rate (partial response only; none had a complete response) was 26%, with a median duration of response of 17.1 months. The OS rate at 6- and 12-months was 85% and 63%, respectively, with PFS rates of 39% and 34%, respectively. Approximately 30% of patients experienced a grade 3–5 drug-related adverse event. The panel voted to include pembrolizumab for patients with previously treated, PD-L1–positive recurrent or metastatic NPC for the 2018 update, but this is a category 2B option based on panel consensus.

Combination and single-agent systemic therapy regimens recommended by the panel for patients with recurrent, unresectable, or metastatic NPC can be found on CHEM-A 2 of 5, page 485.

Radiation Therapy

Intensity-modulated RT (IMRT) is now widely used in H&N cancers and is the predominant technique used at NCCN Member Institutions.[63,64] It is useful in reducing long-term toxicity in H&N cancers and particularly NPC by reducing the dose to ≥1 major salivary glands, temporal lobes, mandible, auditory structures (including the cochlea), and optic structures.[65–69] IMRT may help to preserve the optic pathway in patients with sinonasal malignancies.[65] A prospective Korean study showed that 3-dimensional and IMRT techniques were superior to 2-dimensional radiation for both PFS and OS, and IMRT was associated with improved survival in multivariate analysis, particularly in T3–T4 tumors.[70]

Proton therapy has also been used to treat sinonasal malignancies.[71–73] A systematic review and meta-analysis of 41 noncomparative observation studies suggested that patients with malignant diseases of the nasal cavity and paranasal sinuses who received proton therapy had statistically superior disease-free survival at 5 years and locoregional control at longest follow-up than those receiving IMRT. Compared with all photon-treated patients, patients with sinonasal malignancies who received charged particle therapy had significantly more neurologic toxic effects, although the authors noted a strong possibility of reporting bias, with significantly more particle therapy articles reporting toxic effects.[74] More recent reports show that proton-beam therapy for treatment of sinonasal cancer is associated with good locoregional control, freedom from distant metastasis, and acceptable toxicity.[75,76] Specifically for NPC, proton therapy has established dosimetric superiority, although trials are ongoing to determine the level of clinical benefit.[77] However, without high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other modern radiation techniques, such as IMRT. For the 2018 NCCN Guidelines update, the panel added a statement that proton therapy may be considered for treatment of NPC when normal tissue constraints cannot be met by photon-based therapy (see NASO-A, page 483).

For early-stage high-risk NPC, radiation doses of 66 to 70.2 Gy given with standard fractions are necessary for control of the primary tumor and involved lymph nodes (see NASO-A, page 483). Limited prospective evidence supports elective radiation volume reductions for very early-stage patients.[78] The local control rate for these tumors ranges from 80% to 90%, whereas T3–T4 tumors have a control rate of 30% to 65% with RT alone.[79,80] Radiation dose-fractionation schedules may vary slightly depending on institutional preference. Usually, these deliver between 2.0 and 2.12 Gy/fraction daily (Monday–Friday) for 33 to 35 fractions to all areas of gross disease to a total dose of approximately 70 Gy.[81] Low-risk subclinical disease in the low neck is often treated with 44 to 54.1 Gy at 1.64 to 2.0 Gy per fraction, and for intermediate-risk disease 59.4 to 63 Gy in 1.8 to 2.0 Gy per fraction is often given with dose-painting to different regions of the skull base and neck. International guidelines have been recently published describing the design of radiation clinical target volumes.[82]

Follow-Up/Surveillance for NPC

Recommendations for surveillance following treatment of NPC include a complete H&N examination, endoscopic examination, and supportive care and rehabilitation. Because the deep areas of the skull base may be inaccessible to clinical examination, periodic cross-sectional imaging may be necessary. The clinical benefit of blood EBV DNA monitoring is currently uncertain (see "Epstein-Barr Virus," page 482), but it may be considered (category 2B). Within the immediate several months after treatment with either RT or CRT, evaluation with imaging (eg, CT and/or MRI with contrast, FDG-PET/CT) guides the use of neck dissection.[83–86] The rare patient who completes all therapy with residual disease in the neck and experiences a complete response at the primary should undergo a neck dissection.

Conclusions

Although NPC is a relatively rare cancer, there are areas of endemic incidence in some areas of the world. Infection with EBV is implicated in the development of endemic-type NPC. Patients with ear-

ly-stage NPC should be treated with RT. For those with locoregionally advanced NPC, the panel recommends concurrent CRT with additional chemotherapy (either before or after CRT). For patients with M1 disease, recommended initial therapy options include either a platinum-based combination systemic therapy regimen or CRT for patients with limited metastatic burden and advanced locoregional disease. For the 2018 update, the panel voted to include pembrolizumab for patients with previously treated, PD-L1–positive recurrent or metastatic NPC (category 2B). When RT is used to treat patients with NPC, proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy, although IMRT is preferred.

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Posttest Questions

1. For a patient with stage III NPC, which chemotherapy agent is recommended in the NCCN Guidelines for H&N Cancers to be given concurrently with RT?
   a. Carboplatin
   b. Cisplatin
   c. Docetaxel
   d. Vinorelbine
   e. Any of the above

2. True or False: For patients with locoregional NPC, studies have shown that high initial levels of plasma EBV DNA, or persistently elevated levels near or at the end of RT, are associated with better outcomes following RT or CRT.

3. For a patient with stage IVb NPC, which treatment option is recommended as a category 1 option in the NCCN Guidelines for H&N Cancers:
   a. Carboplatin/cetuximab
   b. Cisplatin/gemcitabine
   c. Gemcitabine
   d. Pembrolizumab
   e. Vinorelbine