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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

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Head and Neck Cancers, Version 2.2025
Featured Updates to the NCCN Guidelines

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Abstract

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

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Overview

Nasopharyngeal carcinoma (NPC) is a relatively uncommon cancer, with an estimated 120,434 new cases and 73,482 deaths reported in 2022.[1] However, certain regions of the world are affected by endemic disease, with the highest global incidence rates occurring in Southeast Asia (particularly southern China), Micronesia/Polynesia, Eastern Asia, and North Africa.[1] The incidence rates are 2 to 3 times higher in men than in women.[2] Infection with the Epstein-Barr virus (EBV) is a key etiologic factor in the development of NPC.[3,4] Among head and neck cancers, endemic NPC has one of the highest tendencies to metastasize to distant sites, with approximately 1 in 10 patients presenting with distant metastases.[5] However, with the advent of modern radiotherapy (RT) techniques as part of initial treatment, locoregional recurrences of endemic NPC have become uncommon, occurring in <10% of patients, except in those with the most locally advanced cancers.[6]

The NCCN Guidelines for Head and Neck Cancers provide recommendations for the evaluation and management of NPC, addressing the risks of local, regional, and distant disease. Recent updates to these guidelines include revisions to systemic therapy recommendations based on emerging evidence in the field.

Treatment

The most recent clinical trial data on the treatment of NPC are limited to EBV-associated disease. Prospective studies that include patients with EBV-negative disease are largely lacking, or are only represented as nonprospectively defined subsets, primarily in studies conducted in the United States before EBV testing became routine for eligibility and monitoring in NPC clinical trials.[7]

Early-Stage and Locoregionally Advanced Disease

The Intergroup trial 0099, which randomly assigned patients to external-beam RT (EBRT) with concurrent cisplatin plus adjuvant chemotherapy with cisplatin and 5-FU (PF) for 3 cycles versus EBRT alone (patients not separated by EBV status), closed early

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

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment.

The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

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

when an interim analysis disclosed a highly significant survival advantage favoring the combined chemotherapy and RT group.[8] The addition of chemotherapy also decreased local, regional, and distant recurrence rates. This study was conducted in the United States, and subsequent phase III randomized trials in Asia confirmed that concurrent chemoradiation (chemoRT) without adjuvant PF similarly increased survival in endemic-area populations when compared with RT alone.[9–12] In one of these trials, 5-year overall survival (OS) was 70% for the chemoRT group versus 59% for the RT group.[9] A randomized study conducted in Singapore, which was modeled after the Intergroup 0099 treatment regimen, confirmed the benefit of adding concurrent platinum to RT with adjuvant PF, using a multiday infusion of platinum instead of a single bolus high-dose approach.[11] One of the largest phase III randomized trials ever conducted in NPC comparing concurrent cisplatin/RT with (or without) adjuvant PF showed that adjuvant chemotherapy did not significantly improve survival following chemoRT (hazard ratio [HR], 0.74 [95% CI, 0.49–1.10]; P=.13).[13]

Advanced radiation techniques are recommended for curative-intent treatment of NPC and to minimize the long-term side effects that are common in survivors. IMRT is now preferred due to its ability to encompass all areas of cancer spread, which can be located in close proximity to the brainstem, temporal lobes, cochleae, and optic nerves and chiasm. Randomized trials evaluating the optimal use of concurrent systemic therapy/RT for locoregionally advanced NPC were largely completed prior to the routine practice of intensity-modulated RT (IMRT), under earlier-era staging systems. Meta-analyses published in 2017 and 2018 showed that the addition of chemotherapy to IMRT did not improve survival outcomes in stage II disease (ie, T0–2N1 and T2N0) compared with IMRT alone.[14–16] A multicenter randomized phase II trial from China also showed that the addition of concurrent chemotherapy to IMRT did not significantly improve survival outcomes or disease control in patients with stage II NPC (n=84).[17] The combined treatment was also associated with increased incidence of leukopenia (P=.022). Another multicenter randomized phase II trial from China, which also evaluated the addition of concurrent chemotherapy to IMRT, showed that IMRT alone was noninferior to IMRT with concurrent cisplatin in 341 patients with T3N0 disease and no adverse features (all nodes <3 cm, no involvement of level IV/IVb nodes, no extranodal extension, and EBV DNA <4,000 copies/mL).[18] However, because this was a single phase II study powered based on a 10% noninferiority margin, many practitioners continue to use chemoRT for T3N0M0 disease.

An individual patient data meta-analysis by Blanchard et al[19] that included 19 trials and 4,806 patients with nonmetastatic NPC showed that both adjuvant chemotherapy following chemoRT and chemoRT without adjuvant chemotherapy were associated with better OS (HR, 0.65 [95% CI, 0.56–0.76] and 0.80 [95% CI, 0.70–0.93], respectively) and progression-free survival (PFS; HR, 0.62 [95% CI, 0.53–0.72] and, 0.81 [95% CI, 0.71–0.92], respectively) than RT without concurrent systemic therapy. However, differences between the included studies assessing chemoRT 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. The NRG-HN001 trial (ClinicalTrials.gov identifier: NCT02135042), a phase II/III study, aimed to investigate whether delivery of adjuvant chemotherapy should be eliminated or intensified based on the status of EBV DNA plasma levels after chemoRT. This trial was closed slightly prematurely due to slowing accrual; as of March 2024, insufficient events had occurred to evaluate the value of the postradiation serum EBV DNA level as a biomarker for adjuvant treatment decision-making.

Substantial evidence supports the use of induction chemotherapy followed by concurrent systemic therapy/RT for treatment of locoregionally advanced NPC. Two randomized phase III trials from China published in 2019 showed a survival benefit for induction chemotherapy followed by concurrent systemic therapy/RT compared with concurrent systemic therapy/RT alone.[20,21] Results from multiple systematic reviews suggest that induction chemotherapy prior to systemic therapy/RT in patients with locally advanced NPC may potentially impact tumor control compared with systemic therapy/RT without additional

chemotherapy.[22–25] However, these reviews had inconsistent results when evaluating the impact on survival. Based on comparisons with systemic therapy/RT alone, induction chemotherapy appears to perform better than adjuvant chemotherapy for some outcomes, such as reduction of distant metastases.[26]

Currently available evidence generally favors the addition of induction chemotherapy to concurrent systemic therapy/RT in patients with locoregionally advanced NPC defined as T stage ≥T3 or N stage ≥N2.[22–25,27] A 2017 network meta-analysis based on an individual patient data meta-analysis (including 20 trials and 5,144 patients) showed that the addition of adjuvant chemotherapy to chemoRT was associated with better PFS (HR, 0.81 [95% CI, 0.66–0.98]), compared with chemoRT only.[22] The authors argued that more chemotherapy, in addition to concurrent chemoRT, could reduce recurrence rates. A 2023 update to this meta-analysis, which included 28 trials and 8,214 patients, continued to show that both induction chemotherapy and adjuvant chemotherapy were superior to systemic therapy/RT alone, but induction chemotherapy was associated with greater benefit for distant progression (HR, 0.66 [95% CI, 0.47–0.93] and 0.65 [95% CI, 0.53–0.80] for induction chemotherapy with and without taxanes, respectively).[27] A 2017 meta-analysis including 27 trials with 7,940 patients showed that induction chemotherapy prior to systemic therapy/IMRT ranked best for OS, PFS, and distant failure-free survival, although head-to-head comparisons with other treatment sequences (10 evaluated, including systemic therapy/RT, induction chemotherapy prior to systemic therapy/RT, and systemic therapy/RT followed by adjuvant chemotherapy, all with IMRT or 2D/3D RT) were not performed.[28] A randomized phase III trial from the Hong Kong NPC Study Group showed a survival benefit when comparing induction chemotherapy prior to systemic therapy/RT to systemic therapy/RT followed by adjuvant chemotherapy (PF), regardless of the induction regimen used (either PF or cisplatin/capecitabine).[29] The induction chemotherapy sequence was also associated with better distant control compared with the adjuvant chemotherapy arm. However, this study was underpowered due to the small number of patients in each study arm. Based upon the aggregate data, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) support the use of induction over adjuvant chemotherapy in patients with locoregionally advanced NPC. A randomized noninferiority phase III trial including 383 patients with locoregionally advanced NPC showed that, following induction using 3 cycles of dose-modified TPF (docetaxel 60 mg/m^2, cisplatin 60 mg/m^2, 5-FU 3,000 mg/m^2), RT without low-dose concomitant cisplatin (30 mg/m^2/week) was noninferior to RT with concomitant cisplatin for 3-year PFS (76.2% vs 76.8%, respectively; HR, 0.92 [95% CI, 0.65—1.32]; P=.66).[30] Grade 3 or 4 adverse events were reported more frequently in the patients who received RT with concomitant cisplatin (73%) compared with patients who received RT alone (54%). The challenge of this study is that dose-modified TPF is less widely used than gemcitabine plus cisplatin (GC) as induction, and the doses of concurrent weekly cisplatin used were lower than the standard, which is 40 mg/m^2/wk or 100 mg/m^2 every 21 days. Therefore, these data have not changed recommendations concerning the use of concurrent cisplatin following induction chemotherapy in this setting.

Three trials have reported on the adjuvant use of capecitabine following standard chemoRT of locoregionally advanced NPC, with improvements in survival outcomes reported.[31–33] The vast majority of patients treated on the low-dose metronomic adjuvant capecitabine study had received both induction chemotherapy and concurrent chemoRT, supporting this adjuvant approach even in patients heavily pretreated with sequential chemoRT.[33]

In summary, currently available evidence favors the addition of either induction or adjuvant chemotherapy to concurrent systemic therapy/RT compared with systemic therapy/RT alone in patients with locoregionally advanced NPC. Evidence suggests that induction chemotherapy may be associated with a greater benefit for distant progression, and this is the preferred approach in the NCCN Guidelines for locally advanced NPC. The routine use of adjuvant capecitabine following either induction and chemoRT or chemoRT alone is less established. Due to concerns about escalating toxicity, ongoing investigations aim to more precisely identify which groups of patients with NPC can safely be offered less-intensive regimens.

Although several trials have studied the addition of immune checkpoint inhibitors to sequential chemoRT in patients with locoregionally advanced NPC, none has demonstrated an OS advantage.[34,35] Therefore, it is premature to consider the addition of checkpoint inhibitor therapy for these patients.

NCCN Recommendations

Treatment recommendations for early-stage and locoregionally advanced NPC can be found in Figure 1. Patients with an unknown primary site after appropriate workup but harboring cervical lymph nodal squamous cell carcinoma that is EBV-positive may be treated in the same manner as those with locoregionally advanced NPC. For other EBV-associated NPC, the principles of treatment can mostly be outlined according to stage. Patients with T1N0M0 nasopharyngeal tumors should be treated with definitive RT alone. Because T2N0 disease is less likely to progress to distant metastasis compared with T2N1 disease, definitive RT alone could be used; concurrent systemic therapy may be indicated in the presence of high-risk features, such as bulky tumor volume or high serum EBV DNA copy number.[36,37] Induction chemotherapy followed by systemic therapy/RT is preferred for advanced locoregional disease (ie, T3N1–N3; T4N0–3; or T0–2N2–3 disease). For patients who did not receive induction chemotherapy, adjuvant chemotherapy following treatment with concurrent systemic therapy/RT is recommended. The use of capecitabine as adjuvant treatment following induction and concurrent chemoRT is supported by current evidence.[33] Concurrent systemic therapy/RT alone is recommended for patients with T0–2N1 disease and can be considered for select patients with lower-risk T3N0 disease, who were excluded from randomized trials evaluating the benefits of adjuvant and induction chemotherapy.[13,20,21,38] Induction or adjuvant chemotherapy may be considered for these patients in the presence of high-risk features, including, for example, a high blood EBV DNA level, which may indicate worse prognosis. The recommended use of blood EBV DNA levels is complicated by lack of standardization and harmonization of these assays, and therefore the NCCN panel is unable to recommend specific quantitative guidance concerning their interpretation. For NPC that is not virally driven, similar principles are applied, although it may be a consideration that these tumors are generally more prone to local relapse and have lower rates of distant metastases.

When induction chemotherapy is used, GC[21,39] and modified TPF[38] are both preferred options for patients with EBV-

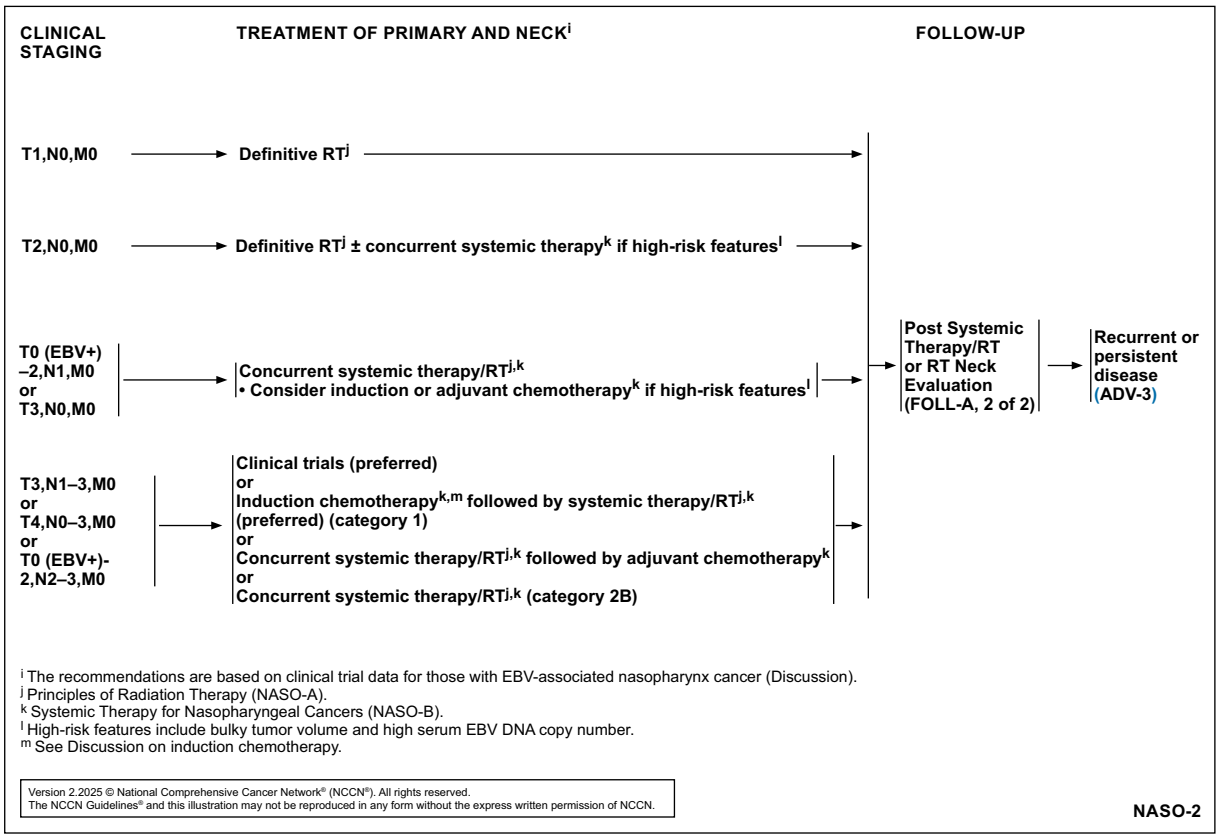

Figure 1. NASO-2. NCCN Clinical Practice Guidelines in Oncology for Head and Neck Cancers, Version 2.2025.

related NPC. Other induction/sequential chemotherapy regimens are included in the NCCN Guidelines for Head and Neck Cancers based on lower-level evidence. The use of induction for patients with non–EBV-related NPC remains undefined, because all trials studying induction in NPC were in patients with EBV-related NPC. When using induction chemotherapy for non–EBV-related NPC, it may be equally reasonable to use regimens established in other sites of non–EBV-related squamous cell carcinoma of the head and neck, such as TPF.

The panel recommends concurrent systemic therapy/RT (cisplatin) with either induction or adjuvant chemotherapy for locoregionally advanced NPC, favoring induction over adjuvant in the clinical scenarios discussed earlier. Concurrent cisplatin with RT is recommended for all patients who do not have a contraindication to the drug, because the vast majority of randomized trials support the use of cisplatin in this setting.[8,9] If using adjuvant chemotherapy, the preferred option remains PF. Use of metronomic capecitabine as an adjuvant chemotherapy option for treatment of stage III–IVa disease (excluding T3–4N0 and T3N1) is supported by a randomized phase III trial (discussed earlier).[33] The substitution of carboplatin or other platinum substitutes for cisplatin in induction, concurrent, and adjuvant regimens, while studied to some extent,[40–42] should be limited to cisplatin-ineligible patients.

Metastatic Disease

Treatment recommendations for distantly metastatic (M1) NPC can be found in Figure 2.

Population-based data appear to support the role of earlier RT in the management of metastatic NPC,[43] but treatment ultimately depends on whether the disease is localized or widespread and if it is symptomatic or posing a clinical risk to the patient.[8,9,40] For patients with oligometastatic disease, potentially curative therapy (ie, RT alone or surgery) is indicated if the patient is fit (ECOG 0–1); this locoregionally focused approach is often used following robust antitumor effects observed with systemic chemotherapy.[44,45]

In a multicenter randomized phase III trial, patients (n=126) with de novo metastatic NPC who achieved a complete response or partial response after the first 3 cycles of PF and with good performance status (PS) were randomized to receive or not receive consolidative locoregional IMRT directed at the primary and nodal gross disease to total doses of 70 Gy after completion of 6 planned cycles.[46] The IMRT arm was associated with improved 24-month OS (76.4% vs 54.5%) and PFS compared with chemotherapy alone. Based on the results of this study, RT at a definitive dose level to the primary site and involved regional nodes is recommended for patients with oligometastatic NPC if complete response (or near complete response) is achieved with systemic therapy. However, it should be noted that the role of consolidative radiation has yet to be completely established in the current era where immunochemotherapy has now become the recommended initial treatment in the first-line metastatic setting.

In a randomized phase III trial evaluating the efficacy and safety of maintenance capecitabine following induction chemotherapy in 104 patients with newly diagnosed metastatic NPC,

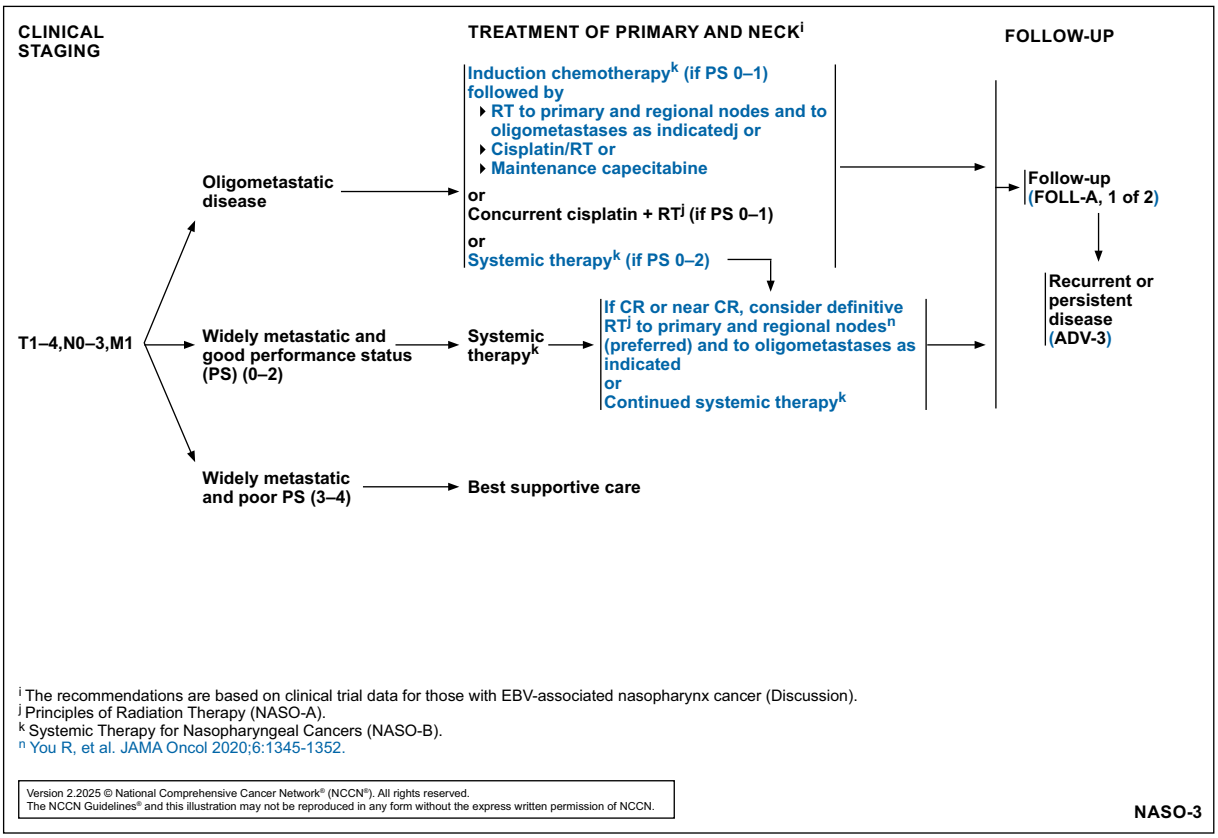

Figure 2. NASO-3. NCCN Clinical Practice Guidelines in Oncology for Head and Neck Cancers, Version 2.2025.

median PFS was greater in patients who received maintenance capecitabine compared with those who received best supportive care alone (35.9 vs 8.2 months, respectively).[32] The objective response rate (25.0% vs 11.5%, respectively) and median duration of response (40.0 vs 13.2 months, respectively) both favored the maintenance capecitabine arm, as well, compared with best supportive care alone. Based on study results, maintenance capecitabine without concurrent RT following induction chemotherapy is an option for patients with metastatic oligometastatic disease (PS 0–1 only).

GC is recommended for first-line therapy for patients with metastatic NPC based on category 1 level evidence demonstrating a survival advantage over PF.[47,48] See later discussion of immunotherapy. Because the data for GC demonstrating superiority to PF come from an era when GC was not typically used for induction, the superiority of GC over PF in patients who have had prior exposure to GC is unknown. Other combination regimens for these patients include cisplatin or carboplatin, plus a taxane[49,50]; PF[50,51]; gemcitabine/carboplatin[52]; or carboplatin/cetuximab.[52] Results from a comparison of 5 different cisplatin-based regimens for NPC showed that all had substantial anticancer activity.[53] Active and more commonly used single agents are listed in the algorithm (see Figure 3).[51,54–65]

Toripalimab-tpzi, in combination with GC, is a category 1 preferred option in the NCCN Guidelines for first-line treatment of recurrent or metastatic NPC. Toripalimab, in combination with GC, was evaluated as a first-line therapy option for recurrent or metastatic NPC in the randomized phase III JUPITER-02 trial.[66] Patients from China, Taiwan, and Singapore (n=289) were randomized to receive toripalimab or a placebo. PFS (HR, 0.52) and OS (HR, 0.63) were both significantly greater in the toripalimab arm (median PFS, 21.4 months; median OS, not reached) compared with the placebo arm (median PFS, 8.2, months; median OS, 33.7 months). Adverse events leading to discontinuation of toripalimab or placebo, immune-related adverse events, and grade ≥3 immune-related adverse events were more frequently reported in the toripalimab arm, although overall incidence of adverse events, grade ≥3 adverse events, and fatal adverse events did not significantly differ between the 2 study arms. In addition, toripalimab monotherapy for recurrent or metastatic NPC previously treated with chemotherapy is supported by a nonrandomized phase II study from China (n=190), showing an overall response rate of 20.5%, median duration of response of 12.8 months, median PFS of 1.9 months, and median OS of 17.4 months.[67] Toripalimab-tpzi is therefore a preferred option in the NCCN Guidelines for recurrent or metastatic NPC, for disease progression on or after platinum-containing therapy.

Tislelizumab, in combination with GC, was evaluated as a first-line therapy option for recurrent or metastatic NPC in the randomized phase III RATIONALE-309 trial.[34] Patients from China (n=263) were randomized to receive tislelizumab or a placebo. Interim analyses showed that PFS was significantly greater in the tislelizumab arm compared with the placebo arm (9.2 vs 7.4 months, respectively; HR, 0.52). A phase II indication-expansion study from China including 21 patients with nonkeratinizing NPC that progressed following prior systemic therapy treatment

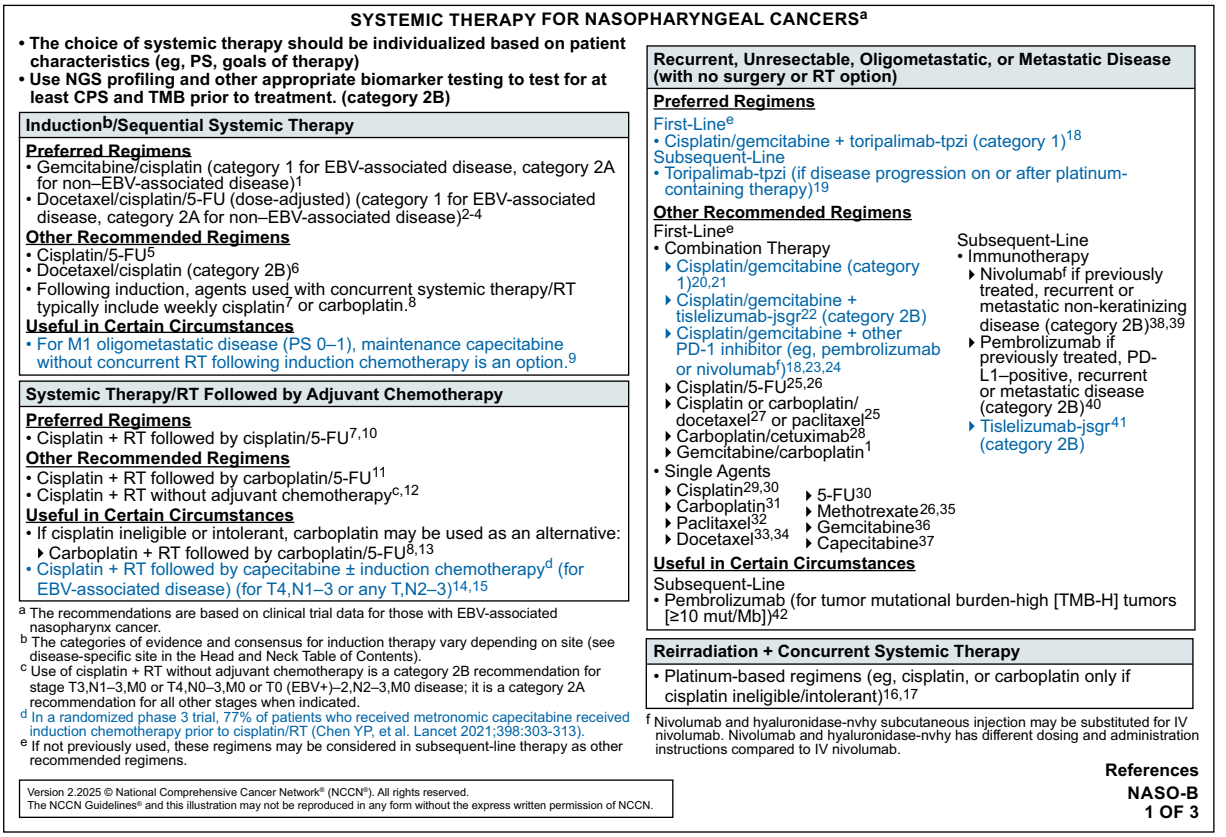

Figure 3. NASO-B 1 of 3. NCCN Clinical Practice Guidelines in Oncology for Head and Neck Cancers, Version 2.2025.

showed an overall response rate of 43% (95% CI, 21.8%–66.0%), a disease control rate of 86% (95% CI, 63.7%–97.0%), median duration of response of 8.3 months, and median PFS of 10.4 months.[68] Based on the results of these trials, tislelizumab-jsgr is a category 2B treatment option in the first-line (in combination with GC) and subsequent-line settings for patients with recurrent or metastatic NPC. This drug is currently not FDA approved for the treatment of NPC.

The PD-1 antibody camrelizumab, administered in combination with GC, has also been evaluated in a randomized phase III trial from China, with a prespecified interim analysis showing significantly greater PFS in the camrelizumab arm compared with the placebo arm (9.7 vs 6.9 months, respectively; HR, 0.54).[69] This agent is not currently available in the United States.

The anti–PD-1 antibodies pembrolizumab and nivolumab have been independently evaluated as monotherapy for previously treated, recurrent or metastatic NPC in nonrandomized trials. 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).[70] All but 2 of the patients had previously received systemic therapy for their recurrent or metastatic disease. The objective response rate (partial response only, because no patients 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. Pembrolizumab is an option for patients with previously treated PD-L1–positive recurrent or metastatic NPC, but this is a category 2B recommendation based on panel consensus. Pembrolizumab is also an option for patients with previously treated tumor mutational burden–high (TMB-H; ≥10 mutations/megabase) disease, based on results from the phase II KEYNOTE-158 trial, although there were no patients with NPC in this study.[71]

Nivolumab as treatment of recurrent or metastatic NPC has been evaluated in phase I/II trials. In the CheckMate 358 trial, nivolumab had an objective response rate of 20.8% and a disease control rate of 45.8% in 24 patients.[72] A Japanese study showed a more modest overall response rate of 16.7% and disease control rate of 41.7%.[73] In an NCI-sponsored trial, 44 patients with previously treated recurrent or metastatic NPC (>80% nonkeratinizing disease) were treated with nivolumab.[74] The objective response rate was 20.5%, 1-year OS was 59%, and 1-year PFS was 19.3%. Based on the results of these trials, nivolumab is a category 2B treatment option for patients with previously treated, recurrent or metastatic nonkeratinizing NPC.

A full list of systemic therapy recommendations for recurrent/metastatic NPC can be found in Figure 3.

Radiation Therapy Dose, Fractionation, and Targets

Radiation dose-fractionation schedules may vary slightly depending on institutional preference (see "Cancer of the Nasopharynx: Principles of Radiation Therapy" in the full version of these NCCN Guidelines at NCCN.org [NASO-A]). Radiation doses of approximately 70 Gy given in standard fractions of approximately 2.0 Gy/fraction are recommended for control of the gross primary tumor and involved lymph nodes; one specific alternative schedule

consists of 2.12 Gy/fraction daily (Monday–Friday) for 33 fractions to all areas of gross disease, also to a total dose of approximately 69.69 Gy.[75] Low-risk subclinical disease, such as in the low neck, can be treated separately to a dose of 44 to 50 Gy at 2.0 Gy/fraction or can be treated simultaneously within the same plan as for gross disease to doses of 54 to 56 Gy at 1.6 to 1.7 Gy/fraction. For areas considered to be at intermediate risk, slightly higher doses such as 59.4 to 63 Gy in 1.8 to 2.0 Gy/fraction can be given to regions of the skull base and neck in proximity to gross disease. The total doses and fractionation should be prescribed in relationship to each other and the overall schedule as part of an integrated plan to address the varying areas at risk.

Some recent initiatives have attempted to reduce treatment volumes. For instance, in a randomized multicenter phase III trial from China (n=446), 5-year regional relapse-free survival did not significantly differ between patients with N0–1 NPC who received elective RT to the ipsilateral upper neck (sparing the uninvolved lower neck) and those who received standard whole-neck irradiation (95.0% vs 94.9%, respectively).[76] Acute radiation-related toxic effects were generally similar between the study arms, although rates of some late toxicities favored the elective upper-neck RT arm, specifically hypothyroidism, skin toxicity, dysphagia, and neck tissue damage.[76,77]

Definitive-style dose-fractionation schedules are frequently used for patients with de novo metastatic disease who achieve response to initial induction therapy and then become eligible for consolidative irradiation of the gross primary and nodal disease. However, for other metastatic scenarios, a variety of palliative schedules may be used (see the full version of these NCCN Guidelines at NCCN.org). For treatment volumes following induction chemotherapy, there are conflicting recommendations,[78] but a common practice is to reduce the volumes receiving the highest dose according to shrinkage of tumor that respects anatomic boundaries.

Reirradiation of locoregionally recurrent NPC should be conducted with careful attention to the previously delivered radiation plan and performed when complete surgical extirpation is not possible.[79] Due to the anatomic location of NPC in proximity to the optic structures, brain, brainstem, and spinal cord, reirradiation carries a high risk of injury to critical neural structures. In a phase III open-label trial from China, patients with locally advanced recurrent NPC (n=144) were randomized to receive hyperfractionated RT (prescription dose of approximately 64.8 Gy in 54 fractions, twice daily with an intrafraction interval of at least 6 hours) or RT with mild hypofractionation (prescription dose of 60 Gy in 27 fractions at 2.22 Gy/fraction, given once per day).[80] Both arms delivered 54 Gy to an expanded target (1 Gy twice daily in the hyperfractionation arm and 2 Gy once daily in the mild hypofractionation arm). The 3-year OS rates were higher in the hyperfractionation arm compared with the mild hypofractionation arm (74.6% vs 55.0%, respectively; HR, 0.54 [95% CI, 0.33–0.88]; P=.014). Although there was no significant difference in locoregional relapse-free survival or distant metastasis-free survival, grade 5 late complications were less frequent in the hyperfractionation arm (7% vs 24%). Because tolerability and late complications are a frequent concern associated with reirradiation, hyperfractionation to a lower total physical dose is a highly appealing option for patients who are able to manage this rigorous twice-daily schedule.

Recommendations regarding NPC reirradiation have been published,[81] and reports describe a variety of technical approaches, including IMRT, stereotactic body RT (SBRT), and brachytherapy.[82–84] In general, a fractionated course of IMRT in combination with concurrent chemotherapy is the most frequently used approach when the intent remains curative, with SBRT or more highly hypofractionated schedules (eg, ≥3 Gy/fraction) being more commonly used in cases of palliative intent.

Summary

There have been several recent updates to the systemic therapy recommendations for NPC in the NCCN Guidelines for Head and Neck Cancers, based on emerging evidence. Updates include clarification regarding the preferred sequence of induction versus adjuvant chemotherapy with concurrent systemic therapy/RT for locoregionally advanced disease, use of maintenance capecitabine, and additional anti–PD-1 antibodies for metastatic disease. Radiation dosing recommendations have also been updated based on new evidence in this area.

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