ASCO special articles

Chemotherapy in Combination With Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline

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abstract

PURPOSE The aim of this joint guideline is to provide evidence-based recommendations to practicing physicians and other healthcare providers on definitive-intent chemoradiotherapy for patients with stage II-IVA nasopharyngeal carcinoma (NPC).

METHODS The Chinese Society of Clinical Oncology (CSCO) and ASCO convened an expert panel of radiation oncology, medical oncology, surgery, and advocacy representatives. The literature search included systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2020. Outcomes of interest included survival, distant and locoregional disease control, and quality of life. Expert panel members used this evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 108 relevant studies to inform the evidence base for this guideline. Five overarching clinical questions were addressed, which included subquestions on radiotherapy (RT), chemotherapy sequence, and concurrent, induction, and adjuvant chemotherapy options.

RECOMMENDATIONS Evidence-based recommendations were developed to address aspects of care related to chemotherapy in combination with RT for the definitive-intent treatment of stage II to IVA NPC.

Additional information is available at www.asco.org/head-neck-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a unique head and neck cancer with an extremely uneven geographic global distribution. Although NPC is fairly uncommon in many jurisdictions, it remains a significant public health problem in East and Southeast Asia, which accounted for more than 70% of the approximate 129,000 new diagnoses worldwide in 2018.[1,2] The nonkeratinizing pathological subtype accounts for more than 95% of NPC cases in endemic areas, which is highly associated with Epstein-Barr virus (EBV) infection, whereas the keratinizing subtype constitutes < 20% of cases worldwide.[2] Despite the relatively lower radiotherapy (RT) sensitivity of the keratinizing compared with nonkeratinizing subtypes, NPC almost exclusively relies on (chemo-)radiotherapy to achieve disease control in most presentations, particularly in the definitive treatment of stage II to IVA disease. Precision in RT contour delineation, planning and delivery, and coordination between chemotherapy and RT are paramount to achieve optimal outcomes for this patient population.

Given the complexity of this malignancy, practitioners will benefit from high-quality evidence-based clinical practice guidelines.[3] This Chinese Society of Clinical Oncology (CSCO) and ASCO joint guideline seeks to highlight significant clinical questions about chemotherapy in combination with RT for the definitive treatment of stage II to IVA NPC, and to provide recommendations on these topics on the basis of published literature and expert panel consensus.

GUIDELINE QUESTIONS

This clinical practice guideline addresses five overarching clinical questions: (1) What are the recommended RT techniques and fractionation regimens for patients with stage II-IVA NPC? (2) What is the recommended chemotherapy sequence in addition to RT for patients with stage II-IVA NPC? (3) What are the recommended chemotherapy options for patients with

THE BOTTOM LINE

Chemotherapy in Combination With Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: Chinese Society of Clinical Oncology and ASCO Guideline

Guideline Questions

1. What are the recommended radiotherapy techniques and fractionation regimens for patients with stage II-IVA nasopharyngeal carcinoma?
2. What is the recommended chemotherapy sequence in addition to radiotherapy for patients with stage II-IVA nasopharyngeal carcinoma?
3. What are the recommended chemotherapy options for patients with nasopharyngeal carcinoma receiving concurrent chemoradiotherapy?
4. What are the recommended chemotherapy options for patients with nasopharyngeal carcinoma receiving induction chemotherapy?
5. What are the recommended chemotherapy options for patients with nasopharyngeal carcinoma receiving adjuvant chemotherapy?

Target Population

Patients with stage II-IVA nasopharyngeal carcinoma.

Target Audience

Medical oncologists, radiation oncologists, clinical oncologists, surgeons, nurses, pathologists, oncology pharmacists, and patients.

Methods

An expert panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations

Radiotherapy

For patients with stage II-IVA nasopharyngeal carcinoma.

Recommendation 1.1. For all patients with nasopharyngeal carcinoma (NPC), intensity-modulated radiotherapy (IMRT) with daily image guidance should be offered. If IMRT is unavailable, patients should be transferred to institutions that could implement IMRT whenever possible (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2. For all patients with NPC, both sequential boost and simultaneous integrated boost radiotherapy may be offered (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.3. For all patients with NPC, a prescribed dose of 70 Gy in 33-35 fractions (2.0-2.12 Gy per fraction) delivered over 7 weeks (once daily, 5 fractions per week) should be offered. Radiation dose may be adjusted according to tumor volume and its response to (chemo-)radiotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.4. For all patients with NPC, gross tumor volume should be carefully delineated. Target delineation should follow consensus guidelines and exploit technical opportunities including image fusion. MRI image fusion with CT for target delineation is mandatory, especially to appreciate the potential tumor extension at the skull base and rule out or confirm the presence of cranial nerve involvement and/or intracranial extension (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.5. For patients with NPC who have undergone induction chemotherapy, the preinduction scan should be fused with the postinduction CT simulation data set to illustrate the initial disease extent. The gross tumor volume should generally follow the preinduction tumor extent, especially within bony anatomy (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.6. The delineation of elective nodal volumes should follow international consensus guidelines and cover the bilateral neck from the retropharyngeal lymph nodes to level IV and V. Level 1b may be omitted in prophylactic volume unless there is involvement of the anterior half of the nasal cavity or if there are level II lymph nodes with extranodal extension or size $>$ 2 cm or bilateral involvement. Omission of lower neck volume in the uninvolved side of the neck may be considered if the neck contains no equivocal lymph node(s) (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

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Chemotherapy Sequence

Recommendation 2.1. For patients with T2N0 (AJCC 8th) NPC, chemotherapy is not routinely recommended, but may be offered if there are adverse features, such as bulky tumor volumes or high EBV DNA copy number (Type: evidence based; harms outweigh benefits; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.2. For patients with T1-2N1 (AJCC 8th) NPC, concurrent chemotherapy may be offered, particularly for T2 N1 patients (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.3. For patients with Stage III-IVA (except T3N0) (AJCC 8th) NPC, induction chemotherapy should be offered in addition to concurrent chemoradiotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.4. For patients with Stage III-IVA (except T3N0) (AJCC 8th) NPC who do not receive induction chemotherapy plus concurrent chemoradiotherapy, then concurrent chemoradiotherapy plus adjuvant chemotherapy should be offered (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

NOTE. There is a lack of head-to-head trials comparing induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy plus adjuvant chemotherapy, thus which sequence performs better in the contemporary era remains uncertain.

Recommendation 2.5. For patients with T3N0 (AJCC 8th) NPC, concurrent chemoradiotherapy should be offered. Adjuvant or induction chemotherapy may also be offered (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Concurrent Chemotherapy

Recommendation 3.1. For all patients with NPC without contraindications, concurrent cisplatin, given weekly (40 mg/m^2) or once every 3 weeks (triweekly) (100 mg/m^2, or at least 80 mg/m^2), should be offered along with radiotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. For all patients with NPC without contraindications, in the concurrent chemotherapy setting, 3 doses of triweekly or 7 doses of weekly cisplatin should be attempted to achieve a cumulative dose of at least 200 mg/m^2 (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3. For patients with NPC with a contraindication to cisplatin, nedaplatin (100 mg/m^2 triweekly) may be offered for concurrent chemoradiotherapy. Other options that may be offered are carboplatin (area under curve [AUC], 5-6 triweekly) or oxaliplatin (70 mg/m^2 weekly) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.4. For patients with NPC with a contraindication to platinum-based chemotherapy, fluoropyrimidines (eg, capecitabine, 5-fluorouracil, and tegafur) with concurrent radiotherapy may be offered (Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Induction Chemotherapy

Recommendation 4.1. For all patients with NPC receiving induction chemotherapy, platinum-based induction regimens should be offered. The following regimens may be used in the absence of medical contraindications: GP (gemcitabine: 1,000 mg/m^2 d1, d8; cisplatin 80 mg/m^2 d1) or TPF (docetaxel 60-75 mg/m^2 d1; cisplatin 60-75 mg/m^2 d1; 5-fluorouracil 600-750 mg/m^2 per day, continuous intravenous infusion d1-5); others include PF (cisplatin 80-100 mg/m^2 d1; 5-fluorouracil 800-1,000 mg/m^2 per day, continuous intravenous infusion d1-5), PX (cisplatin 100 mg/m^2 d1; capecitabine 2000 mg/m^2 per day, d1-14), and TP (docetaxel 75 mg/m^2 d1; cisplatin 75 mg/m^2 d1) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.2. For patients with NPC receiving induction chemotherapy, the regimens should be administered every three weeks for a total of three cycles, or at the minimum two cycles (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.3. For patients with NPC receiving induction chemotherapy, chemoradiotherapy should be commenced within 21-28 days from the first day of the last cycle of induction chemotherapy (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Adjuvant Chemotherapy

Recommendation 5.1. For all patients with NPC receiving adjuvant chemotherapy, PF (cisplatin 80 mg/m^2 d1 or 20 mg/m^2 per day, d1-5; 5-fluorouracil 1,000 mg/m^2 per day, continuous intravenous infusion d1-4, or 800 mg/m^2 per day, continuous

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intravenous infusion d1-5) administered every 4 weeks for a total of 3 cycles should be offered (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.2. For all patients with NPC receiving adjuvant chemotherapy and with a contraindication to cisplatin, carboplatin (AUC 5) may be combined with 5-fluorouracil (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 5.3. For all patients with NPC receiving adjuvant chemotherapy and with a contraindication to platinum-containing chemotherapy, the use of non–platinum-based regimens remains experimental at this time and should not be offered routinely outside the context of a clinical trial (Type: evidence based; harms outweigh benefits; Evidence quality: intermediate; Strength of recommendation: strong).

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

CSCO and ASCO believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

NPC receiving concurrent chemoradiotherapy? (4) What are the recommended chemotherapy options for patients with NPC receiving induction chemotherapy? (5) What are the recommended chemotherapy options for patients with NPC receiving adjuvant chemotherapy?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by an international multidisciplinary expert panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The expert panel included representatives from the CSCO, which was the lead organization on this joint effort. The expert panel, cochaired by J.M. and Y. S., met via teleconference and/or webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the expert panel were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to *Journal of Clinical Oncology (JCO)* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the expert panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by CSCO.

The recommendations were developed by using a systematic review in PubMed (January 1990 to August 2020) of systematic reviews, meta-analyses, and randomized clinical trials (RCTs), and clinical experience. Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria: (1) studies including patients with stage II-IVA NPC and (2) interventions focusing on RT and/or chemotherapy for definitive treatment.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[4] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO and CSCO expert panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of the formal review of the emerging literature, ASCO and CSCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the CSCO and ASCO, Inc, to assist providers in clinical decision making. The information herein should not be relied upon as being complete

or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words such as must, must not, should, and should not indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. CSCO and ASCO provide this information on an as-is basis and makes no warranty, express or implied, regarding the information. CSCO and ASCO specifically disclaim any warranties of merchantability or fitness for a particular use or purpose. CSCO and ASCO assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The expert panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the expert panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting, or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the policy, the majority of the members of the expert panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 108 studies met eligibility criteria and form the evidentiary basis for the guideline recommendations. These included 42 systematic reviews[5-46] and 66 RCTs.[47-112] Identified trials were published between 1990 and August 2020 and focused on RT and/or chemotherapy. The primary outcomes reported in studies on therapeutic interventions included overall survival (OS), progression-free survival (PFS), relapse-free survival (RFS), failure-free survival (FFS), disease-free survival (DFS) as well as distant failure-free survival or control rate, locoregional failure-free survival or control rate, and quality of life. Of note, whereas many of the studies quoted in this article used the American Joint Committee on Cancer (AJCC) 6th or 7th editions, all references to stage in the recommendations in this guideline are based on the current 8th edition of the AJCC staging system.[113] Details on the study characteristics are included in the Supplement (Data Supplement, online only). The systematic review flow diagram is shown in Figure 1.

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed. Study quality was formally assessed for the 66 RCTs identified. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc., generally indicating a low (30%), intermediate (59%), and high (11%) potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results. Refer to the ASCO Methodology Manual (https://www.asco.org/research-guidelines/quality-guidelines/guidelines-tools-resources/guideline-methodology) for more information and for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

CLINICAL QUESTION 1

What are the recommended RT techniques and fractionation regimens for patients with stage II-IVA NPC?

Recommendation 1.1. For all patients with NPC, intensity-modulated radiotherapy (IMRT) with daily image guidance should be offered. If IMRT is unavailable, patients should be transferred to institutions that could implement IMRT whenever possible (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2. For all patients with NPC, both sequential boost and simultaneous integrated boost radiotherapy may be offered (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Compared with conventional 2-dimensional (2D) or 3-dimensional (3D) RT, IMRT enables conformation of tumoricidal doses to

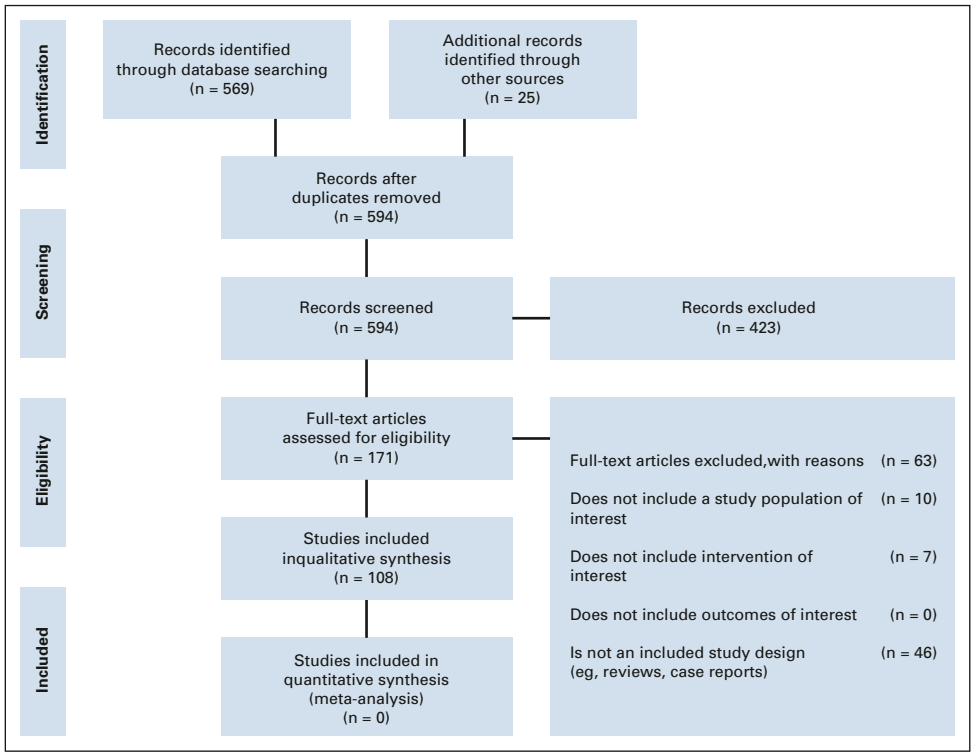

FIG 1. PRISMA diagram.

irregular shaped distributions, thereby providing opportunities for safe delivery of high doses to NPC while protecting adjacent critical structures. The benefit of toxicity reduction with IMRT, such as neurotoxicity, xerostomia, trismus, and dysphagia, has been demonstrated in three RCTs[80,92,95] and multiple meta-analyses.[13,29] One RCT[80] and several meta-analyses have also shown that IMRT enhances disease control and survival in patients with NPC.[11,13,29]

Daily image guidance should be implemented to minimize interfractional setup variation during high-precision radiotherapy. Daily image guidance may also enable customized margin for planning target volumes (PTV) and monitoring of geometric and dosimetric changes during the planned course of RT.[114-118]

IMRT can be delivered using either sequential boost or simultaneous integrated boost technique. A phase III RCT[57] of 209 patients has shown similar efficacy and toxicities with these two approaches. The former allows adaptation of treatment volume to a patient's anatomic changes. The latter is a convenient and resource-saving approach by maintaining a single treatment phase.

Recommendation 1.3. For all patients with NPC, a prescribed dose of 70 Gy in 33-35 fractions (2.0-2.12 Gy per fraction) delivered over 7 weeks (once daily, 5 fractions per week) should be offered. Radiation dose may be adjusted according to tumor volume and its response to (chemo-) radiotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. Outcomes of patients with NPC have improved significantly. However, NPC survivors often suffer from substantial toxicity burdens.[119] RT fraction size is one of the major determinants of late toxicity. The fraction size of 2.0 to 2.12 Gy, five fractions per week, to a total prescribed dose of 70 Gy in 33-35 fractions was used in the Intergroup 0099[110] and RTOG 0225 trials[120] and demonstrated good efficacy with acceptable toxicity. Since patients with residual disease have a poor prognosis,[121,122] for a patient with MRI-detected residual tumor at the end of IMRT, an additional 2-4 Gy boost in 1-2 fractions may be considered. For a very responsive small primary, a slightly lower total dose (eg, 66-68 Gy) may be considered. Larger fraction sizes should be avoided, especially when combined with chemotherapy, because of concerns about substantial late toxicity with unproven efficacy. The Hong Kong NPC-9902[96,123] and NPC-0501[71,124] trials failed to demonstrate a clinical benefit from moderately accelerated fractionation of six fractions versus conventional fractionation of five fractions per week RT. The value of hyperfractionation with twice-daily fractions to increase the total dose while keeping the overall RT duration the same is uncertain in NPC since clinical trials show conflicting results.[81,93,108]

Recommendation 1.4. For all patients with NPC, gross tumor volume should be carefully delineated. Target delineation should follow consensus guidelines and exploit technical opportunities including image fusion. MRI image

fusion with CT for target delineation is mandatory, especially to appreciate the potential tumor extension at the skull base and rule out or confirm the presence of cranial nerve involvement and/or intracranial extension (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. CT and MRI are both important for target delineation in this disease. MRI improves the detection of disease extension at the skull base, perineural disease without bone involvement, marrow infiltration, tumor extension to the paranasal sinuses and orbit, and retropharyngeal lymph node involvement, while CT improves the detection of neck disease and cortical bone invasion.[125,126] The expert panel recommends to follow international consensus guidelines on target and organs at risk contouring[127-129] and IMRT planning,[130] which emphasize the importance of MRI-CT image fusion in gross tumor volume (GTV) delineation, and provide guidance on clinical target volume (CTV) delineation[128] and dose prioritization and acceptance criteria in IMRT planning.[130] The radiation oncologist is encouraged to review the CT or MRI with a head and neck radiologist to appreciate the disease extent and if applicable, the response to induction chemotherapy (IC), especially when uncertainty is aroused.

Recommendation 1.5. For patients with NPC who have undergone induction chemotherapy, the preinduction scan should be fused with the postinduction CT simulation data set to illustrate the initial disease extent. The gross tumor volume should generally follow the preinduction tumor extent, especially within bony anatomy (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. The international consensus guidelines[128] recommend full therapeutic dose to cover preinduction gross tumor extent without exceeding the maximal tolerance of critical structures regardless of response to IC. This is especially important at the skull base because of the difficulty in fully appreciating the disease extent within bony anatomy, lack of salvage options in this location, and uncertain benefit from postinduction volume reduction. A phase III RCT by Yang et al[55] enrolled 212 patients with locally advanced NPC and compared efficacy and toxicities of patients treated with GTV delineated according to postinduction MRI (Post-IC GTV) versus those maintaining the preinduction volume (Pre-IC GTV). While the PTV of Post-IC GTV received 70 Gy in both arms, the PTV of Pre-IC GTV was randomly assigned to receive either 70 Gy in arm A or 64 Gy in arm B. There was no difference in disease control and survival between the two arms. Grade 4 late toxicity was also similar, but the group receiving 64 Gy to Pre-IC GTV had better xerostomia scores and better cognitive function. Therefore, carefully tailoring around the residual GTV after IC may be feasible if the resolved preinduction GTV is fully covered with at least an intermediate dose.

Recommendation 1.6. The delineation of elective nodal volumes should follow international consensus guidelines and cover the bilateral neck from the retropharyngeal lymph nodes to level IV and V. Level 1b may be omitted in prophylactic volume unless there is involvement of the anterior half of the nasal cavity or if there are level II lymph nodes with extranodal extension or size $>$ 2 cm or bilateral involvement. Omission of lower neck volume in the uninvolved side of the neck may be considered if the neck contains no equivocal lymph node(s) (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. NPC has a highly infiltrative nature within the nasopharyngeal mucosa. The CTV delineation should follow international consensus guidelines[128] with attention to any potential routes of spread. To reduce treatment toxicity, modifications of traditional elective volumes, such as sparing the level 1B nodal region or omitting lower neck volumes in the uninvolved side of the neck, have been explored in clinical trials and retrospective cohort studies. Two retrospective studies[131,132] have shown that level 1b-sparing IMRT appears to be safe and feasible, with the exception of patients with level IIA lymph node $\geq$ 2 cm and/or with extranodal extension, N2 disease, or primary tumor extension to areas that drain to level 1b as the first echelon site. The safety of lower neck sparing in uninvolved side of the neck was demonstrated in a meta-analysis,[21] a small RCT for N0 patients,[76] and several retrospective studies.[133-135]

CLINICAL QUESTION 2

What is the recommended chemotherapy sequence in addition to radiotherapy for patients with stage II-IVA nasopharyngeal carcinoma?

Recommendation 2.1. For patients with T2N0 (AJCC 8th) NPC, chemotherapy is not routinely recommended, but may be offered if there are adverse features, such as bulky tumor volumes or high EBV DNA copy number (type: evidence-based; harms outweigh benefits; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 2.2. For patients with T1-2N1 (AJCC 8th) NPC, concurrent chemotherapy may be offered, particularly for T2 N1 patients (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Literature review and clinical interpretation. In the era of conventional 2D-RT, Chen et al[86] reported a randomized study showing significant improvements in 5-year OS and PFS in favor of concurrent chemoradiotherapy (CCRT) over RT alone for stage II NPC. The addition of concurrent chemotherapy reduced distant failure without a significant

improvement in locoregional control over RT alone. However, it should be noted that the study used the Chinese 1992 staging system, and 13% of patients would be reclassified as N2/stage III according to the 7th edition International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification criteria. The 10-year outcomes of this trial were in accordance with the previous report, but suggested that the survival benefits conferred by CCRT were mainly reflected in the T2N1 population.[51] As IMRT has become a routine choice, the role of concurrent chemotherapy is not absolutely defined for stage II NPC, given the paucity of randomly assigned data in the IMRT era. Several meta-analyses,[15,19,24] mainly including retrospective studies, have shown that IMRT alone may achieve equivalent treatment outcomes as compared to CCRT for stage II NPC. Recently, Huang et al[48] described the outcomes of a randomized phase II trial involving 84 patients with stage II NPC. With a median follow-up of 75 months, they observed no superiority of CCRT over IMRT alone for 5-year OS (94% *v* 100%; $P = .25$) and PFS (87% *v* 90%; $P = .72$). Considering that stage II consists of three subgroups (T2N0, and T1-2N1), among which N1 patients are at higher risk of distant metastasis,[136] the results of an ongoing large RCT (CinicalTrials.gov Identifier: NCT02633202) evaluating additional concurrent chemotherapy to IMRT are anticipated to shed light on the appropriate treatment for this subset. Incorporating other prognosticators such as plasma EBV DNA[137,138] may allow risk stratification of this heterogeneous group of patients with stage II NPC and permit optimal chemotherapy tailoring high-risk subset.

Recommendation 2.3. For patients with Stage III-IVA (except T3N0) (AJCC 8th) NPC, induction chemotherapy should be offered in addition to concurrent chemoradiotherapy (type: evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Recommendation 2.4. For patients with Stage III-IVA (except T3N0) (AJCC 8th) NPC who did not receive induction chemotherapy plus concurrent chemoradiotherapy, concurrent chemoradiotherapy plus adjuvant chemotherapy should be offered (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

NOTE. There is a lack of head-to-head trials comparing induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy plus adjuvant chemotherapy, thus which sequence performs better in the contemporary era remains uncertain.

Recommendation 2.5. For patients with T3N0 (AJCC 8th) NPC, concurrent chemoradiotherapy should be offered. Adjuvant or induction chemotherapy may also be offered (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Literature review and clinical interpretation. The landmark Intergroup 0099 randomized trial established chemoradiotherapy as the standard treatment of locoregionally advanced (stage III-IVA) NPC, given the superior survival end points of CCRT plus adjuvant chemotherapy (AC) over RT alone.[110] Subsequent randomized studies from endemic areas confirmed the survival benefit of CCRT with or without AC versus RT alone in locoregionally advanced NPC.[62,75,78,85,98,100-102] An individual patient data (IPD) meta-analysis of 19 RCTs showed that the most significant OS benefits of adding chemotherapy to RT were seen with CCRT either with or without AC.[37] By contrast, if without concurrent chemotherapy, AC or IC plus RT did not yield significant survival benefits as compared with RT alone. Therefore, CCRT is considered the backbone of treatment for locoregionally advanced NPC.

Notably, the Intergroup 0099 trial was conducted in the conventional RT era where locoregional failure dominated. In the IMRT era, patterns of failure have changed and excellent locoregional control has been achieved. Thus, the benefit of the addition of AC following CCRT for NPC becomes controversial. The primary results of a phase III randomized trial[84] revealed no significant difference in all outcome parameters in patients with locoregionally advanced NPC treated with CCRT alone versus CCRT plus AC, and the long-term results[63] confirmed these findings (5-year OS: 80% *v* 83%, $P = .35$; 5-year PFS: 71% *v* 75%, $P = .72$). In another phase III trial,[61] 104 high-risk patients with NPC identified by detectable plasma EBV DNA after RT were randomly assigned to AC using gemcitabine and cisplatin for six cycles, or observation. That study is the first biomarker-driven RCT in NPC. There was neither OS nor PFS improvement with the addition of AC (5-year rate for OS: 64% *v* 68%; $P = .79$; for PFS: 49% *v* 55%; $P = .75$). Several network meta-analyses[23,30,139,140] reported no statistically significant differences in treatment outcomes by adding AC to CCRT, although a favorable trend for CCRT plus AC was observed. The relatively poor tolerance of AC after definitive RT, with 50%-76% of patients typically completing planned AC,[61,84,91,96,98,99,110] may account for the lack of observed benefit in NPC. The ongoing NRG-HN001 trial (CinicalTrials.gov Identifier: NCT02135042) uses post-RT plasma EBV DNA to select candidates for AC and may identify subgroups who may benefit from the addition of AC on the basis of post-RT risk stratification. Metronomic use of capecitabine in AC is also being investigated in a phase III RCT (CinicalTrials.gov Identifier: NCT02958111).

Compared with AC, IC offers several potential advantages, such as earlier relief of symptoms, better tolerance, early eradication of micrometastases, and tumor volume reduction for sparing critical structures.[2,44] However, early

randomized studies[69,83,89] comparing CCRT with or without IC did not consistently demonstrate favorable results regarding additional IC, probably because of the different induction regimens used or insufficient sample size. In recent years, three large-scale multicenter RCTs[49,50,52,64,66] from Guangzhou were reported; the trials used induction docetaxel, cisplatin, and 5-fluorouracil (TPF)[52,66]; cisplatin and 5-fluorouracil (PF)[50,64]; and gemcitabine and cisplatin (GP)[49] regimens, respectively. These studies all confirmed the superiority of the addition of IC to CCRT over CCRT alone for OS, PFS, and distant failure-free survival, whereas locoregional failure-free survival was improved only in the long-term results of the TPF trial.[52,66] An IPD pooled analysis of four aforementioned trials from endemic areas[50,52,64,66,69,89] demonstrated that IC plus CCRT significantly improved OS (hazard ratio [HR], 0.75; 95% CI, 0.57 to 0.99; 6% absolute benefit at 5 years) and PFS (HR, 0.70; 95% CI, 0.56 to 0.86; 9% absolute benefit at 5 years), with the survival benefit mainly resulting from reduced distant failure (HR, 0.68; 95% CI, 0.51 to 0.90; 7% absolute reduction).[22] A small randomized study from Tunisia and France enrolled 83 patients with locoregionally advanced NPC, and also showed improved PFS with the addition of induction TPF, with a significant effect on OS.[60] Therefore, IC plays an important role in addition to CCRT in management of locoregionally advanced NPC in the IMRT era, mainly through improvement in distant control translating into survival benefit.

Nevertheless, it should be noted that most trials evaluating additional IC to CCRT were conducted in endemic areas; the applicability of IC in nonendemic patients with NPC warrants further studies. Besides, which chemotherapy sequence, that is, induction-concurrent or concurrent-adjuvant, performs better in the contemporary era remains uncertain because of a paucity of prospective randomized trial data directly comparing the two approaches. It is only by inferential comparison of trials with CCRT as the control that IC seems to outperform AC in reduction of distant metastasis in patients with locoregionally advanced NPC. In the subgroup analyses of the NPC-0501 trial by Lee et al,[47,71] comparison of IC plus CCRT versus CCRT plus AC in the conventional fractionation group suggested a significant benefit for 5-year OS (84% *v* 72%; $P = .042$) and PFS (78% *v* 62%; $P = .015$) after adjusting for multiple comparisons. A network meta-analysis evaluating the survival benefit of chemoradiotherapy regimens between 2D- or 3D-RT and IMRT[23] showed that IC followed by concurrent IMRT ranked first in probability for OS, PFS, and distant failure-free survival, whereas AC following concurrent IMRT ranked first in probability for locoregional failure-free survival, although no statistically significant differences in these outcomes were observed between the two groups. Future head-to-head trials comparing IC plus CCRT and CCRT plus AC are needed.

As compared to other patients with locoregionally advanced disease, patients with T3N0 NPC have a relatively lower risk of treatment failure.[138] This subgroup was therefore excluded from several RCTs assessing the addition of AC[63,84] or IC to CCRT.[49,50,52,64,66] Given the lack of randomized trial data, the expert panel recommends a detailed discussion of the benefits versus harms of adding AC or IC to CCRT for T3N0 patients.[137,138,141]

CLINICAL QUESTION 3

What are the recommended chemotherapy options for patients with nasopharyngeal carcinoma receiving concurrent chemoradiotherapy?

Recommendation 3.1. For all patients with NPC without contraindications, concurrent cisplatin, given weekly (40 mg/m^2) or triweekly (100 mg/m^2, or at least 80 mg/m^2), should be offered along with RT (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. For all patients with NPC without contraindications, in the concurrent chemotherapy setting, 3 doses of triweekly or 7 doses of weekly cisplatin should be attempted to achieve a cumulative dose of at least 200 mg/m^2 (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3. For patients with NPC with a contraindication to cisplatin, nedaplatin (100 mg/m^2 triweekly) may be offered for concurrent chemoradiotherapy. Other options that may be offered are carboplatin (area under curve [AUC] 5-6 triweekly) or oxaliplatin (70 mg/m^2 weekly) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.4. For patients with NPC with a contraindication to platinum-based chemotherapy, fluoropyrimidines (eg, capecitabine, 5-fluorouracil, and tegafur) with concurrent RT may be offered (Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak),

Literature review and clinical interpretation. The recommendations of triweekly cisplatin of 100 mg/m^2 or weekly cisplatin of 40 mg/m^2 dosing to be delivered concurrently with RT were based on the early randomized phase III trials comparing CCRT with or without AC versus RT alone.[62,78,86,98,100,110] These trials established the superiority of chemoradiotherapy over RT for locoregionally advanced NPC. Of note, three trials[62,98,110] used the triweekly regimen, whereas two trials[78,100] used the weekly regimen; one trial by Chen et al[86] used weekly cisplatin of 30 mg/m^2 for 7 cycles. Head-to-head comparisons between both regimens have been performed. A small randomized phase II study by Lee at al[67] showed no significant differences in efficacy and toxicity profiles between the once weekly (40 mg/m^2) and triweekly (100 mg/m^2) schedules of cisplatin, and the weekly cisplatin regimen appeared to be associated with improved quality of life. Likewise, a large-

scale phase III RCT (ClinicalTrials.gov Chinese Clinical Trial Register identifier: ChiCTR-TRC-12001979) enrolled 526 patients with locoregionally advanced NPC, and the preliminary results suggested no difference in survival outcomes, but there were increased incidences of leukopenia (27.3% *v* 16.2%) and thrombocytopenia (4.8% *v* 1.2%) for the weekly regimen (40 mg/m^2 × 6) compared with the triweekly (100 mg/m^2 × 2) schedule.[142] The final results of that study may aid complete assessment of the different dosing schedules. Of note, the total dose in the triweekly schedule was lower (200 mg/m^2) compared with the weekly regimen (240 mg/m^2).

Evidence, however, suggests that the cumulative dose of cisplatin may play a more important role than cisplatin schedule for efficacy. In this regard, no level 1 data exist to guide the optimal dose intensity of concurrent cisplatin, although post hoc analyses of phase III trials suggest that a threshold of cumulative dose of 200 mg/m^2 is required for efficacy.[17,123,143] If IC is given in addition to CCRT, retrospective data show that the cumulative cisplatin dose needed in CCRT phase is typically 160 mg/m^2 on the basis of patient tolerance of cumulative cisplatin.[144-146] For patients in whom cisplatin is contraindicated, other alternative concurrent agents include carboplatin (area under the curve [AUC] 5-6),[87,94,147] oxaliplatin (70 mg/m^2 weekly),[97] and nedaplatin (100 mg/m^2 triweekly).[56] If platinum-based chemotherapy is contraindicated, fluoropyrimidines such as UFT (uracil and tegafur in a 4:1 M ratio)[101] may also be offered as an option.

CLINICAL QUESTION 4

What are the recommended chemotherapy options for patients with nasopharyngeal carcinoma receiving induction chemotherapy?

Recommendation 4.1. For all patients with NPC receiving induction chemotherapy, platinum-based induction regimens should be offered. The following regimens may be used in the absence of medical contraindications: GP (gemcitabine: 1,000 mg/m^2 d1, d8; cisplatin 80 mg/m^2 d1) or TPF (docetaxel 60-75 mg/m^2 d1; cisplatin 60-75 mg/m^2 d1; 5-fluorouracil 600-750 mg/m^2 per day, continuous intravenous infusion d1-5); others include PF (cisplatin 80-100 mg/m^2 d1; 5-fluorouracil 800-1,000 mg/m^2 per day, continuous intravenous infusion d1-5), PX (cisplatin 100 mg/m^2 d1; capecitabine 2000 mg/m^2 per day, d1-14), and TP (docetaxel 75 mg/m^2 d1; cisplatin 75 mg/m^2 d1) (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong).

Literature review and clinical interpretation. A 2009 published randomized phase II study[89] first observed significant improvement in 3-year OS from 68% to 94% (HR, 0.24; 95% CI, 0.08 to 0.73) by adding two cycles of induction docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) before CCRT in NPC. Subsequently, two large-scale phase III RCTs[49,52,66] demonstrated the efficacy of induction TPF (60 mg/m^2 docetaxel, 60 mg/m^2 cisplatin, and 600 mg/m^2 5-fluorouracil as a continuous 120-hour infusion; every 3 weeks for three cycles) and GP (1,000 mg/m^2 gemcitabine on days 1 and 8, and 80 mg/m^2 cisplatin; every 3 weeks for three cycles) in locoregionally advanced NPC (except T3-4N0), respectively. In the TPF trial,[52,66] the 5-year OS (HR, 0.65; 95% CI, 0.43 to 0.98), PFS (HR, 0.65; 95% CI, 0.43 to 0.98), distant failure-free survival (HR, 0.60; 95% CI, 0.38 to 0.95), and locoregional failure-free survival (HR, 0.58; 95% CI, 0.34 to 0.99) were all significantly improved in the IC plus CCRT group as compared to the CCRT alone group. Despite the 20% dose reduction of each drug compared with that in another trial (75 mg/m^2 docetaxel, 75 mg/m^2 cisplatin, and 750 mg/m^2 5-fluorouracil as a continuous 120-hour infusion),[60] a high incidence of grade 3 or 4 acute toxicities such as neutropenia (35%), leukopenia (27%), and diarrhea (8%) was observed. In the other trial,[49] the induction GP regimen also showed benefits for 3-year OS (HR, 0.43; 95% CI, 0.24 to 0.77), PFS (HR, 0.51; 95% CI, 0.34 to 0.77), and distant failure-free survival (HR, 0.43; 95% CI, 0.25 to 0.73), but locoregional control was not significantly improved. Relatively good tolerance was shown for GP, with incidence of grade 3 or 4 neutropenia, leukopenia, and diarrhea of 21%, 11%, and 0.4%, respectively. Other recommended induction regimens included PF (80-100 mg/m^2 cisplatin and 800-1,000 mg/m^2 5-fluorouracil as a continuous 120-hour infusion) and cisplatin plus capecitabine (PX; 100 mg/m^2 cisplatin and 2000 mg/m^2 capecitabine daily for 14 days).[47,50,64,71]

There is a paucity of randomly assigned data comparing different induction regimens directly. A recent randomized, noninferiority trial enrolling 278 patients with locoregionally advanced NPC suggested similar treatment efficacy of the TPF and PF regimens.[148] The indirect comparisons of an IPD meta-analysis detected no significant differences between different IC regimens, that is, such as TPF, TP, and PF,[22] whereas another IPD network meta-analysis of 28 trials involving 8,214 patients indicated that IC with taxanes ranked better than IC without taxanes for OS, although no statistically significant difference was shown.[149] Therefore, the IC regimen could be selected based on the patient's status. Whether replacing cisplatin with other platinum agents such as lobaplatin or nedaplatin or replacing 5-fluorouracil with capecitabine during the induction phase can maintain noninferior efficacy with improved quality of life is under evaluation (ClinicalTrials.gov clinical trial information: ChiCTR-TRC-13003285, NCT03503136).

Recommendation 4.2. For patients with NPC receiving induction chemotherapy, the regimens should be administered every 3 weeks for a total of 3 cycles, or at the minimum 2 cycles (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong).

Recommendation 4.3. For patients with NPC receiving induction chemotherapy, chemoradiotherapy should be commenced within 21-28 days from the first day of the last cycle of induction chemotherapy (type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Literature review and clinical interpretation. Two or three cycles of IC are recommended, and three cycles are more commonly used, although there are no randomly assigned data on the efficacy of different cycles. A retrospective study suggested that additional cycles to two cycles of IC were not associated with improved treatment outcomes for patients with NPC.[47] Real-time monitoring of EBV DNA during IC may also inform on tumor response for therapeutic adaptation,[48] but more prospective data are warranted. Given the absence of prospective literature evaluating the impact of the interval between IC and RT on survival in NPC, the expert panel recommends that patients should start RT within 3-4 weeks from the first day of the last IC cycle to minimize the risk of treatment failure. This is supported by a retrospective analysis that reported that a prolonged interval $>$ 30 days was associated with unfavorable prognosis.[49]

CLINICAL QUESTION 5

What are the recommended chemotherapy options for patients with nasopharyngeal carcinoma receiving adjuvant chemotherapy?

Recommendation 5.1. For all patients with NPC receiving adjuvant chemotherapy, PF (cisplatin 80 mg/m^2 d1 or 20 mg/m^2 per day, d1-5; 5-fluorouracil 1,000 mg/m^2 per day, continuous intravenous infusion d1-4, or 800 mg/m^2 per day, continuous intravenous infusion d1-5) administered every 4 weeks for a total of 3 cycles should be offered (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. Results of the Intergroup study set a standard of three cycles AC with PF (cisplatin 80 mg/m^2 on day 1 and 5-fluorouracil 1,000 mg/m^2 on days 1-4, continuous 96-hour infusion, repeated every 4 weeks) after definitive CCRT.[110] Several large randomized trials confirmed the superiority of CCRT plus AC to RT alone for locoregionally advanced NPC.[62,78,85,98] Both drugs can be delivered with minor modification without changing the dose intensity, that is, dividing cisplatin dose of 80 mg/m^2 over 4 consecutive days (20 mg/m^2 day 1-4) by the Singapore group[2] or changing 5-fluorouracil administration from a daily dose of 1,000 mg/m^2 for 4-day continuous infusion to a daily dose of 800 mg/m^2 for 5-day infusion by the Guangzhou group.[78,84] These modifications are intended to reduce the acute toxicities of the regimen. Of note, the original design of PF regimen in head and neck cancer was cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil 1,000 mg/m^2 on days 1-5, continuous 120-hour infusion, repeated every 3 weeks in the neoadjuvant setting.[150] In consideration of poor tolerance to adjuvant therapy after definitive CCRT in NPC, this regimen was adjusted with not only a 20% reduction of dose intensity for both drugs but also changing delivery schedule from every 3 weeks to every 4 weeks per cycle in all these trials. Despite these modifications, only 55% of patients could complete the planned three cycles of AC in the Intergroup study,[110] and a range of 46%-78% completion rate was reported in other trials.[62,71,78,84,85,98,120] The pooled data of 441 patients with locoregionally advanced NPC treated in the Hong Kong trials NPC-9901 and NPC-9902 showed that the total dose of 5-fluorouracil during AC was significantly associated with the distant failure-free rate by multivariate analysis.[151] Thus, current evidence recommends completing three cycles of PF regimen for patients who need adjuvant therapy by an experienced team.

Recommendation 5.2. For all patients with NPC receiving adjuvant chemotherapy and with a contraindication to cisplatin, carboplatin (AUC 5) may be combined with 5-fluorouracil (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation Replacing cisplatin with carboplatin is also acceptable if cisplatin is contraindicated.[94,152] A single-center randomized, noninferiority trial compared the Intergroup regimen above to carboplatin infusion of 100 mg/m^2 concurrent with RT followed by carboplatin (AUC 5 intravenously) and 5-fluorouracil (100 mg/m^2/day over 96 hours) in 206 patients with NPC. Forty-two percent of patients in the cisplatin group completed the three cycles of AC compared with 73% in the carboplatin group. Similar survival outcomes were shown; nephrotoxicity, leukopenia, and anemia were more common in the cisplatin group, whereas thrombocytopenia was more common in the carboplatin arm. The same group also conducted a multicenter randomized trial to compare concurrent chemoradiation with carboplatin to the same regimen with adjuvant carboplatin and 5-fluorouracil in 175 patients with T2N0-T4N2M0 NPC (UICC/AJCC 7th edition).[152] The addition of adjuvant carboplatin-fluorouracil resulted in significantly improved 2-year disease-free survival.

Recommendation 5.3. For all patients with NPC receiving adjuvant chemotherapy and with a contraindication to platinum-containing chemotherapy, the use of non–platinum-based regimens remains experimental at this time and should not be offered routinely outside the context of a clinical trial (Type: evidence based; harms outweigh benefits; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. CCRT plus AC remains an option for locoregionally advanced NPC. While IC improved distant control, CCRT plus AC had superior local control presumably from accelerated repopulation associated with induction strategies.[153-159]

In the NPC-0501 trial,[71,124] induction PF showed no significant differences with adjuvant PF, despite the higher doses, dose density, and better tolerability of IC, whereas the induction cisplatin-capecitabine arm performed better. Several retrospective studies reported significant OS improvements with a metronomic oral fluorouracil drug as AC.[160-163] Metronomic chemotherapy refers to treatment at regular intervals with substantially lower doses over prolonged periods.[164] The high compliance and low toxicities of metronomic chemotherapy render this strategy appealing for AC in patients with NPC after completing radical CCRT. A phase 3 trial of metronomic adjuvant capecitabine has completed the accrual (CinicalTrials.gov identifier: NCT02958111), whereas another testing UFT is ongoing (CinicalTrials.gov identifier: NCT02363400). As aforementioned, the main criticism of AC is tolerability. Metronomic oral fluorouracil or the use of other drug regimens as AC may address this issue. Besides, alternative treatment options for platinum unsuitable patients were provided in other head and neck cancers[165]; but the current use of non–platinum-based regimens remains experimental in NPC, and cannot be routinely recommended.

Figure 2 provides visual interpretations of these recommendations in the management algorithm.

PATIENT AND CLINICIAN COMMUNICATION

Several retrospective studies have identified a survival benefit in patients with NPC treated in high-volume institutions.[166-168] The improvement likely reflects the availability of expertise and resources (medication, equipment, and personnel), protocol adherence, peer-reviewed quality assurance processes, as well as multidisciplinary coordination and supportive care in these institutions. For a clinician who is not familiar with the management of NPC or a facility lacking such resources, it is encouraged to seek expert advice or to refer the patient to an institution with expertise and resources available to deliver high-precision (chemo-)radiotherapy, including institutions beyond their local or regional area of residence. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[169]

HEALTH DISPARITIES

Although this CSCO and ASCO clinical practice guideline represents expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[170-173] All over the world, many patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and healthcare providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[174,175] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[176,177]

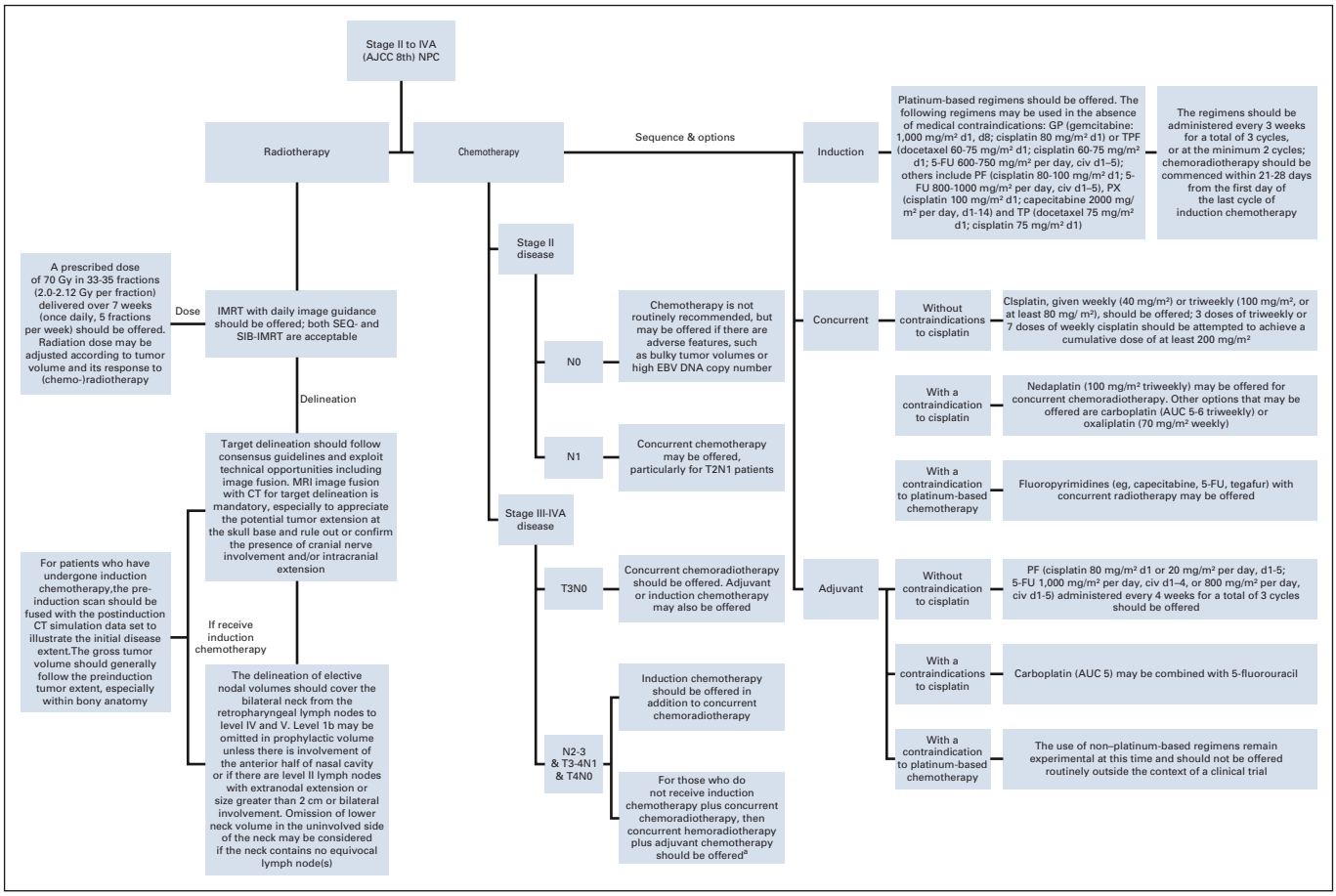

FIG 2. Treatment algorithm of stage II-IVA nasopharyngeal carcinoma. [a]There is a lack of head-to-head trials comparing induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy plus adjuvant chemotherapy. AJCC, American Joint Committee on Cancer; AUC, area under curve; civ, continuous intravenous infusion; EBV, Epstein-Barr virus; FU, fluorouracil; IMRT, intensity-modulated radiotherapy; NPC, nasopharyngeal carcinoma; SEQ-IMRT, sequential IMRT; SIB-IMRT, simultaneous integrated boost IMRT.

Discussion of cost can be an important part of shared decision making.[178] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[178]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware of the fact that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[178]

As part of the guideline development process, CSCO and ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data; agents that are not currently available in either China or the United States or Canada; and/or are industry-sponsored. No cost-effectiveness analyses were identified to inform the topic.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from August 10, 2020, through August 24, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with forty written comments received from 13 respondents. Most of the responses received either agreed or agreed with slight modifications to the recommendations and few of the respondents disagreed. Expert panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation

revisions. All changes were incorporated prior to CPGC review and approval.

GUIDELINE IMPLEMENTATION

This CSCO and ASCO guideline is developed for implementation across health settings. A member from ASCO's Practice Guideline Implementation Network (PGIN) is included on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. Specifically, cochairs from CSCO are responsible for the implementation of this guideline in China. Finally, it should be noted that majority of the studies included in this guideline are from endemic regions, and future trials are warrant to confirm the applicability of the recommendations to nonendemic patients with NPC. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

CSCO and ASCO believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[179] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[169] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Role of Treatment Deintensification in the Management of p16 + Oropharyngeal Cancer[180] (http://ascopubs.org/doi/10.1200/JCO.19.00441)
- Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx[181] (http://ascopubs.org/doi/10.1200/JCO.18.01921)
- Human Papillomavirus Testing in Head and Neck Carcinomas[182] (http://ascopubs.org/doi/10.1200/JCO.18.00684)
- Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck[183] (http://ascopubs.org/doi/10.1200/JCO.20.00275)

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EDITOR'S NOTE

This Chinese Society of Clinical Oncology (CSCO) and American Society of Clinical Oncology (ASCO) Joint Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/head-neck-cancer-guidelines.

EQUAL CONTRIBUTION

J.M. and Y.S. were expert panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Chemotherapy in Combination With Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: Chinese Society of Clinical Oncology and ASCO Guideline

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Treatment of NPC Expert Panel Membership

Name	Affiliation or Institution	Role or Area of Expertise
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Yu-Pei Chen	Sun Yat-sen University Cancer Center, Guangzhou, China	Clinical Oncology
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Jun-Lin Yi	National Cancer Center, Beijing, China	Clinical Oncology
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Brigette Ma	The Chinese University of Hong Kong, Hong Kong, China	Medical Oncology
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Robert Haddad	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Ying Sun (cochair)	State Key Laboratory of Oncology in South China, China	Radiation Oncology
Sue S. Yom	University of California San Francisco, San Francisco, CA	Radiation Oncology
Jin-Yi Lang	Sichuan Cancer Hospital & Institute, Chengdu, China	Radiation Oncology
Chao-Su Hu	Fudan University Shanghai Cancer Center, Shanghai, China	Radiation Oncology
Melvin L. K. Chua	National Cancer Centre Singapore, Singapore	Radiation Oncology
Joseph T. S. Wee	National Cancer Centre Singapore, Singapore	Radiation Oncology
Anne W. M. Lee	The University of Hong Kong, Hong Kong	Radiation Oncology
Quynh-Thu Le	Stanford University School of Medicine, Stanford, CA	Radiation Oncology
Nancy Lee	Memorial Sloan Kettering Cancer Center, New York, NY	Radiation Oncology
Shao Hui Huang	Princess Margaret Cancer Centre, Toronto, ON, Canada	Radiation Oncology
Jatin Shah	Memorial Sloan Kettering Cancer Center, New York, NY	Surgical Oncology
Alexander C. Whitley	Central Alabama Radiation Oncology, Montgomery, AL	Community Oncology (PGIN Representative)
Thomas J. Morgan	Monmouth, NJ	Patient Representative
Nofisat Ismaila	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)