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Guideline Endorsement 5-7 Version 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

An Endorsement of the 2021 Guideline on Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline

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An assessment conducted in December 2023 deferred the review of Guideline Endorsement 5-7 Version 3. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

You can access the full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/551

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Section 1: Guideline Endorsement

GUIDELINE OBJECTIVES

The objectives of the guideline are to make recommendations regarding the addition of neoadjuvant/concurrent/adjuvant chemotherapy to chemoradiotherapy in the management of locally advanced squamous cell or undifferentiated nasopharyngeal cancer (NPC) and to identify the optimal chemotherapeutic regimen that improves overall survival. Our recommendations are based on the 2021 Guideline on Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline [1].

TARGET POPULATION

Newly diagnosed patients, eligible for chemotherapy, with locally advanced squamous cell or undifferentiated NPC (stage III or IV).

INTENDED USERS

Healthcare providers involved in the management of NPC patients.

ENDORSEMENT

The Chemotherapy and Radiotherapy for Nasopharyngeal Cancer Development Group (GDG) of Ontario Health (Cancer Care Ontario) endorses the Chinese Society of Clinical Oncology (CSCO)/American Society of Clinical Oncology (ASCO) recommendations of Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline modified by the endorsement process described in this document. They were reprinted with the permission of Wolters Kluwer Health, Inc. and Copyright Clearance Center.

Sixteen of the 21 CSCO/ASCO recommendations were endorsed without changes. Four (R 1.1, R 3.3, R 4.1, R 5.1) recommendations were endorsed with modifications and/or clarifications and one recommendation (R 3.4) was not endorsed (see Table 1-1).

Table 1-1. Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline

Recommendations	Assessment
Radiotherapy (For patients with stage II-IVA NPC)	
R 1.1. For all patients with NPC, IMRT with daily image guidance should be offered. If IMRT is unavailable, patients should be transferred to institutions that could implement IMRT whenever possible. **Modification:** VMAT is a reasonable alternative to IMRT and may be preferred in this setting.	**Endorsed (with modification)**
R 1.2. For all patients with NPC, both sequential boost and simultaneous integrated boost radiotherapy may be offered (Type: evidence based; benefits outweigh harms.	**Endorsed**
R 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 seven weeks (once daily, 5 fractions per week)	**Endorsed**

should be offered. Radiation dose may be adjusted according to tumour volume and its response to (chemo-)radiotherapy.	
R 1.4. For all patients with NPC, gross tumour 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 tumour extension at the skull base and rule out or confirm the presence of cranial nerve involvement and/or intracranial extension.	**Endorsed**
R 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 tumour volume should generally follow the preinduction tumour extent, especially within bony anatomy.	**Endorsed**
R 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).	**Endorsed**
Chemotherapy sequence	
R 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 tumour volumes or high EBV DNA copy number.	**Endorsed**
R 2.2. For patients with T1-2N1 (AJCC 8th) NPC, concurrent chemotherapy may be offered, particularly for T2 N1 patients.	**Endorsed**
R 2.3. For patients with stage III-IVA (except T3N0) (AJCC 8th) NPC, induction chemotherapy should be offered in addition to concurrent chemoradiotherapy.	**Endorsed**
R 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. 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.	**Endorsed**
R 2.5. For patients with T3N0 (AJCC 8th) NPC, concurrent chemoradiotherapy should be offered. Adjuvant or induction chemotherapy may also be offered.	**Endorsed**
Concurrent Chemotherapy	
R 3.1. For all patients with NPC without contraindications, concurrent cisplatin, given weekly (40 mg/m^2) or once every three weeks (triweekly) (100 mg/m^2, or at least 80 mg/m^2), should be offered along with radiotherapy.	**Endorsed**
R 3.2. For all patients with NPC without contraindications, in the concurrent chemotherapy setting, three doses of triweekly or seven doses of weekly cisplatin should be attempted to achieve a cumulative dose of at least 200 mg/m^2.	**Endorsed**
R 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). **Clarification and Modification:** The recommendation is endorsed for carboplatin only. Carboplatin plus infusional fluorouracil is also considered an acceptable alternative based on its activity in NPC and generalized from the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) [2].	**Endorsed (with clarification and modification)**

R 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. **Explanation:** This is not typically done in Canadian clinical practice and the quality of the evidence is weak.	**Not Endorsed (with explanation)**
Induction chemotherapy	
R 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: 1000 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 800-1000 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). **Clarification:** In the absence of head-to-head comparisons, based on familiarity to clinicians, toxicity profile, and technical ease of administration, GP is the preferred regimen for EBV-related NPC.	**Endorsed (with clarification)**
R 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.	**Endorsed**
R 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.	**Endorsed**
Adjuvant chemotherapy	
R 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 1000 mg/m^2 per day, continuous intravenous infusion d1-4, or 800 mg/m^2 per day, continuous intravenous infusion d1-5) administered every four weeks for a total of three cycles should be offered. **Modification:** Use of GP for a total of three cycles as adjuvant therapy is a reasonable alternative to PF.	**Endorsed (with modification)**
R 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.	**Endorsed**
R 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.	**Endorsed**
Abbreviations: AJCC = American Joint Committee on Cancer; ASCO = American Society of Clinical Oncology; AUC = area under curve; CSCO = Chinese Society of Clinical Oncology; CT = computerized tomography; d = day; DNA = deoxyribonucleic acid; EBV = Epstein Barr virus; IMRT = intensity-modulated radiotherapy; MRI = magnetic resonance imaging; NPC = nasopharyngeal carcinoma; VMAT = volumetric modulated arc therapy	

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Section 2: Endorsement Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario) (OH [CCO]). The Program in Evidence-based care mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The Program in Evidence-based is a provincial initiative of Ontario Health (Cancer Care Ontario) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR GUIDELINE

During the annual document assessment and review, this guideline was identified as needing an update because the recommendations no longer reflect current practice. Current practice standards include using radiotherapy with concurrent cisplatin-based chemoradiation to treat locally advanced squamous cell or undifferentiated NPC. The question now is whether the use of neoadjuvant chemotherapy and/or adjuvant chemotherapy after chemoradiotherapy is worthwhile.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Chemotherapy and Radiotherapy for Nasopharyngeal Cancer GDG, which was convened at the request of the Head and Neck Cancer Advisory Committee (CAC). The project was led by a small Working Group of the GDG, which was responsible for reviewing the evidence base and recommendations in "Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II-IVA" in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in medical oncology, radiation oncology, and pathology. Other members of the Chemotherapy and Radiotherapy for Nasopharyngeal Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

ENDORSEMENT METHODS

The Program in Evidence-based care endorses guidelines using the process outlined in Ontario Health (Cancer Care Ontario)'s Guideline Endorsement Protocol [3]. This process includes selection of a guideline, assessment of the recommendations (if applicable), drafting of the endorsement document by the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The Program in Evidence-based care assesses the quality of guidelines using the AGREE II tool [4]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour

and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations may be provided along with the recommendations for information purposes.

Selection of Guidelines

The following sources were initially searched for existing guidelines in September 2020 with the search term(s) nasopharyngeal cancer, chemotherapy, radiotherapy: National Institute for Health and Care Excellence Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki. In March 2021 a newly published guideline was brought to the attention of the Working Group and the group accepted it as potentially useful and relevant to guide practice in Ontario. A decision was made to halt the ongoing Program in Evidence-based systematic review underway at the time and endorse the 2021 Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline.

Assessment of Guideline(s)

The Working Group selected the CSCO/ASCO guideline because the rigour of development domain, which assesses the methodological quality of the guideline, had the highest score.

Details of the AGREE II assessment can be found in Appendix 2. The overall quality of the guideline was rated as "6" by one appraiser and "7" by the other (on a scale of 1 to 7). Both appraisers stated that they would recommend this guideline for use. The AGREE II quality ratings for the individual domains were varied; they were assessed at 97% for scope and purpose, 86% for stakeholder involvement, 89% for rigour of development, 89% for clarity of presentation, 92% for applicability, and 92% for editorial independence.

DESCRIPTION OF ENDORSED GUIDELINE(S)

The CSCO/ASCO guideline (published on-line January 2021) assessed treatment options with chemotherapy in combination with radiotherapy for patients with stage I-IVA NPC [1]. As pointed out by the authors "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 [5]. Despite the relatively lower radiotherapy 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"[1].

The guideline recommendations were based five clinical questions and assessed on the basis of a systematic literature review and expert consensus. Forty-two systematic reviews and 66 randomized controlled trials published between 1990 and August 2020 were included, focusing on radiotherapy techniques and fractionation regimens, chemotherapy sequence in addition to radiotherapy, chemotherapy options for patients receiving concurrent chemoradiotherapy, options for patients receiving induction chemotherapy, and options for patients receiving adjuvant chemotherapy [1]. A complete list of recommendations from the CSCO and ASCO guideline are presented in Table 1-1.

ENDORSEMENT PROCESS

The Working Group assessed the 2021 CSCO/ASCO Guideline in detail and reviewed each recommendation of the guideline to determine whether it could be endorsed, endorsed with modifications, or rejected. There are 21 recommendations based on five research questions. The Working Group considered the following issues for each of the recommendations:

1) Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2) Are modifications required to align with the Ontario context?
3) Is it likely there is new, unidentified evidence that would call into question the recommendation?
4) Are statements of qualification/clarification to the recommendation required?

ENDORSEMENT REVIEW AND APPROVAL

Internal Review

For the endorsement document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. The Expert Panel may specify that approval is conditional, and that changes to the document are required.

External Review

Feedback on the approved draft endorsement document is obtained from content experts through Professional Consultation. Relevant care providers and other potential users of the endorsement document are contacted and asked to provide feedback on the recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the Ontario Health (Cancer Care Ontario) website. Ontario Health (Cancer Care Ontario) - Program in Evidence-based Care guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

UPDATING THE ENDORSEMENT

Ontario Health (Cancer Care Ontario)/Program in Evidence-based Care will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ENDORSEMENT and MODIFICATIONS

Sixteen of the 21 CSCO/ASCO recommendations were endorsed without changes. Four (R 1.1, R 3.3, R 4.1, R 5.1) recommendations were endorsed with modifications and/or clarifications and one recommendation (R 3.4) was not endorsed (Table 2-1). See Section 1, Table 1-1 for a list of all 21 recommendations.

Table 2-1. Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline	
Recommendations	**Assessment**

R 1.1. For all patients with NPC, IMRT with daily image guidance should be offered. If IMRT is unavailable, patients should be transferred to institutions that could implement IMRT whenever possible. **Modification:** VMAT is a reasonable alternative to IMRT and may be preferred in this setting.	**Endorsed (with modification)**
R 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). **Clarification and Modification:** The recommendation is endorsed for carboplatin only. Carboplatin plus infusional fluorouracil is considered an acceptable alternative based on its activity in NPC generalized from the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) [2].	**Endorsed (with clarification and modification)**
R 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. **Explanation**: This is not typically done in clinical practice and the quality of the evidence is weak.	**Not Endorsed (with explanation)**
R 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: 1000 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 800-1000 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). **Clarification:** In the absence of head-to-head comparisons, based on familiarity to clinicians, toxicity profile, and technical ease of administration, GP is the preferred regimen for EBV-related NPC.	**Endorsed (with clarification)**
R 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 1000 mg/m^2 per day, continuous intravenous infusion d1-4, or 800 mg/m^2 per day, continuous intravenous infusion d1-5) administered every four weeks for a total of three cycles should be offered. Modification: Use of GP for a total of three cycles as adjuvant therapy is a reasonable alternative to PF.	**Endorsed (with modification)**
Abbreviations: AJCC = American Joint Committee on Cancer; ASCO = American Society of Clinical Oncology; AUC = area under curve; CSCO = Chinese Society of Clinical Oncology; EBV = Epstein Barr virus; IMRT = intensity-modulated radiotherapy; MRI = magnetic resonance imaging; NPC = nasopharyngeal carcinoma; VMAT = volumetric modulated therapy	

ACKNOWLEDGEMENTS

The Chemotherapy and Radiotherapy for Nasopharyngeal Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- Jonathan Sussman and Sheila McNair for providing feedback on draft versions.
- Sara Miller for copy editing.

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Section 3: Internal and External Review

INTERNAL REVIEW

The endorsement was evaluated by the GDG Expert Panel (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

EXPERT PANEL REVIEW AND APPROVAL

Following the formulation of the first draft, the recommendation endorsement was reviewed by the Director and Assistant Director of the Program in Evidence-based and the Working Group was responsible for ensuring the necessary changes were made. An Expert Panel of clinical content experts (members of the head and neck community) reviewed the draft endorsement document, provided feedback, and approved the final version (See Appendix 1 for a list of Expert Panel members and conflict of interest declarations).

All nine members of the GDG Expert Panel voted, for a total of 100% response in September 2021. All nine GDG members approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 3-1.

Table 3-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Yes, I approve it with the following comments and changes • **For R3.3,** the clarification and modification to allow carboplatin and infusion fluorouracil in the concurrent setting has never been tested when given before adjuvant chemotherapy or after induction chemotherapy in NPC. The MACH-NC meta-analysis is relevant for squamous cell cancers and not for undifferentiated nasopharyngeal cancer. I would suggest that these limitations/caveats be considered by the committee and be further clarified in the recommendation. • **For R4.3,** the clarification to allow for "delay for restaging with MRI to assess response prior to radiation planning" needs to have a maximum acceptable delay – e.g. one would think that beyond 35 days for first day of last cycle of induction chemotherapy should not be considered acceptable. • **For R5.1,** it should be added that for patients who cannot tolerate cisplatin, carboplatin may be considered as a reasonable alternative (either with infusional fluorouracil in the adjuvant PF	• This point is noted. The hazard ratios for the overall survival benefit of adding monotherapy cisplatin or platinum/5-fluorouracil concomitant with radiation in the MACH-NC were identical (0.75) (Pignon 2009). As both carboplatin and 5-fluorouracil are active agents in nasopharyngeal cancer, this combination is unlikely to ever be tested in a clinical trial n comparison to cisplatin, and practitioners are familiar with carboplatin/5-fluorouracil it is reasonable to extrapolate similar benefit in this less common scenario. • Agreed. Statement modified to *"Timely initiation of chemoradiotherapy is endorsed, however, delay for restaging with MRI to assess response prior to radiation planning up to 35 days is reasonable" (this statement removed from document after external review [see Table 3.3 below for subsequent changes made during external review]).* • R 5.2 addresses carboplatin. Please see CSCO/ASCO guideline for infusional 5-fluorouracil references.

regimen; or with gemcitabine in the adjuvant GP regimen). Also in this same recommendation, please clarify the reference source to give 5-fluorouracil 800 mg/m^2 per day on days 1-5 every four weeks, as opposed to 1000 mg/m^2 per day on days 1-4 every four weeks. In clinical practice, most patients can only tolerate 800 mg/m^2 per day on days 1-4 every four weeks.	
2. Yes, I approve it with the following comments and changes • Regarding R 4.1. Do we want to denote that DPYD testing is recommended at this time? • Regarding R 4.3. (Clarification) Do we want to note the options of chemotherapy but lack of head-to-head trials?	• DPYD testing prior to fluoropyrimidine-based chemotherapy should be addressed for all patients receiving these drugs with guideline recommendations; however, it is out of scope for this specific guideline. • Agreed. Statement modified to *"In the absence of head-to-head comparisons, based on familiarity to clinicians, toxicity profile, and technical ease of administration, GP is the preferred regimen for EBV-related NPC."*
3. I approve these guidelines with one general comment. • R 4.1 indicates many different allowable "induction" chemotherapy regimens but the clarification states that only gemcitabine (G) and cisplatin (C) is endorsed and the others are not. There seems to be a disconnect with those two statements. Either you should say GC is preferred and others are allowable or do not indicate the others as allowable at all. The clarification says other regimens are not endorsed indicating that they are not allowable. Please try to reconcile this gap.	Agreed. See modification above.

EXTERNAL REVIEW

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the endorsement document. All head and neck oncologists in the Program in Evidence-based database were contacted by email to inform them of the survey (n=67). Five of the 67 approached (7.5%) indicated that they were interested in participating. Four of the non-responders stated that they did not have interest in this area or were unavailable to review this endorsement document at the time; the remaining non-responders did not give a reason. The results of the feedback survey from five clinicians are summarized in Table 3-2. The main comments from the consultation and the Working Group's responses are summarized in Table 3-3.

Table 3-2. Responses to four items on the professional consultation survey.

	N=5 (7.5% of those approched)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				3	2
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1	1	3
3. I would recommend this guideline for use in practice.				2	3
4. What are the barriers or enablers to the implementation of this guideline report?	No barriers anticipated I see no appreciable barriers to its implementation. Barriers could be funding banding/wording of regimens used for N-acetylcysteine for this disease and education of surgeons/radiation oncologists regarding earlier referral for neo--adjuvant discussion.				

Table 3-3. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. R4.3 is ambiguous. There is a lack of consistency with respect to the interval between "first day of last cycle of induction chemotherapy", recommended as "chemoradiotherapy should be commenced within 21 to 28 days," and the modification to accommodate delay in obtaining restaging MRI. The language shifts to allow delay "up to 35 days prior to radiation planning," (planning, not start of chemoradiotherapy). If this is allowed, then the interval to start of chemoradiation could be extended by as much as a further 14 days (up to 49 days) when the interval between radiation planning and start of chemoradiation is added. Is this what the Committee wishes? For consistency, and to encourage minimum delays, I would recommend that the second part of this item be amended to read "delay for restaging MRI etc should be allowed only if chemoradiotherapy can be started within 35 days from the first day of the last cycle of induction chemotherapy."	We agree and have endorsed the recommendation as originally written in the EAU guideline ("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") (see Table 3.1 above for previous changes made during internal review).

CONCLUSION

The final endorsed recommendations contained in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Members of the Chemotherapy and Radiotherapy for Nasopharyngeal Cancer Guideline Development Group

Name	Affiliation	Conflict of Interest
Working Group		
Judy Brown	Health Research Methodologist McMaster University, Department of Oncology, Program in Evidence-Based Care, Hamilton, ON	None declared
Cheryl Ho	BC Cancer Agency Vancouver, BC	[a] See below
Sara Kuruvilla	London Regional Cancer Program 800 Commissioners Road East London, ON	None declared
Bibianna Purgina	Department of Pathology and Laboratory Medicine The Ottawa Hospital/University of Ottawa Ottawa, ON	None declared
Eric Winquist	London Health Sciences Centre - London Regional Cancer Program 790 Commissioners Rd E, London, ON	[b] See below
Khaled Zaza	Queen's University, School of Medicine Department of Oncology	None declared
Expert Panel and Members of the Guideline Development Group		
John de Almeida	Department of Otolaryngology-Head & Neck Surgery University of Toronto	None declared
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Ezra Hahn	Princess Margaret Cancer Centre University Health Network Toronto, Ontario	None declared
Justin Lee	Juravinski Cancer Centre 699 Concession Street Hamilton ON	None declared
Brandon Meyers	Juravinski Cancer Centre 699 Concession Street Hamilton ON	[c] See below
Ian Poon	Sunnybrook Health Sciences Centre 2075 Bayview Avenue Room T2 134 Toronto ON	[d] See below
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Lillian Siu	Princess Margaret Cancer Centre University Health Network Toronto, Ontario	[e] See below
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[a] Paid $500. or more to act in a consulting capacity (BMS, Bayer, AZ ESMO, Pfizer, Eli Lilly, Roche, Merck). Received grants from Boehringer Ingelheim, Sanofi-Genzyme, AstraZeneca, and Eisai.
[b] Paid $500. or more to act in a consulting capacity (Amgen, AstraZeneca, Bayer, Eisal, Merck, Roche).
[c] $500. or more in single year to act in consulting capacity (Merck).
[d] Received relevant business entity provide you or your spouse within last year (Radiation oncologist, Odette Cancer Centre, Sunnybrook Health Science Centre); $500. or more in single year to act in consulting capacity (Advisory Board for AstraZeneca and Sanofi); Principal Investigator for a clinical trial involving any of the objects of study (optimizing head and neck tumour and symptom control in patients unable to tolerate curative intent RT: A Phase III trial comparing Stereotactic Body Radiation Therapy (SBRT) to standard palliative radiation treatment (ON-TASC Study) Approved by CTC/CCTG).
[e] Received relevant business entity provide you or your spouse within last year (cofounder [spouse]: Treadwell Therapeutics); $500. or more in single year to act in consulting capacity (Consulting/advisory arrangements (self): with Merck, Pfizer, Celgene, AstraZeneca, Morphosys, Roche, Oncorus, Symphogen, Seattle Genetics, GlaxoSmithKline, Voronoi, Arvinas, Tessa, Navire, Relay, Rubius, Janpix, Daiichi Sanyko.); Stocks, bonds, or stock options valued at $500 or more in a relevant business entity (Agios); Received any grants or other research support (nIstitution receives clinical trials research support from: Novartis, Bristol-Myers Squibb, Pfizer, Boerhinger-Ingelheim, GlaxoSmithKline, Roche/Genentech, Karyopharm, AstraZeneca, Merck, Celgene, Astellas, Bayer, Abbvie, Amgen, Symphogen, Intensity Therapeutics, Mirati Therapeutics, Shattucks, Avid).

Appendix 2: Agree II Score Sheet

Domain	Item	AGREE II Appraiser Ratings[1]	
		1	2
1) Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	7
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	6
Domain score[2] - (41-6/42-6)*100 = 35/36 *100 = .9722 *100 = **97.2%**		Score 41	
2) Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	5	6
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	6
	6. The target users of the guideline are clearly defined.	7	7
Domain score[2] - (37-6/42-6)*100 = 31/36 *100 = .8611*100 = **86.1%**		Score 37	
3) Rigor of development	7. Systematic methods were used to search for evidence.	6	7
	8. The criteria for selecting the evidence are clearly described.	7	6
	9. The strengths and limitations of the body of evidence are clearly described.	6	5
	10. The methods for formulating the recommendations are clearly described.	6	7
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	5	7
	12. There is an explicit link between the recommendations and the supporting evidence.	7	6
	13. The guideline has been externally reviewed by experts prior to its publication.	7	7
	14. A procedure for updating the guideline is provided.	6	6
Domain score[2] - (101-16/112-16)*100 = 85/96 *100 = .8888 *100 = **88.8%**		Score 101	
4) Clarity of presentation	15. The recommendations are specific and unambiguous.	6	7
	16. The different options for management of the condition or health issue are clearly presented.	5	7
	17. Key recommendations are easily identifiable.	6	7
Domain score[2] - (38-6/42-6)*100 = 32/36 *100 = .8888 *100 = **88.9%**		Score 38	
5) Applicability	18. The guideline describes facilitators and barriers to its application.	6	5
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	5	6
	20. The potential resource implications of applying the recommendations have been considered.	5	6
	21. The guideline presents monitoring and/ or auditing criteria.	6	4
Domain Score[2] - (43-8/56-8)*100 =35/48 *100 = .9210 *100 = **92.1%**		Score 43	

Domain	Item	AGREE II Appraiser Ratings[1]	
		1	2
6) **Editorial independence**	22. The views of the funding body have not influenced the content of the guideline.	6	7
	23. Competing interests of guideline development group members have been recorded and addressed.	6	7
Domain Score[2] - (26-4/28-4)*100 = 22/24 *100 = .9167 *100 = **91.7%**		Score 26	
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**7**	**6**
Overall Guideline Assessment	2. I would recommend this guideline for use.	**Yes**	**Yes**

[1] Rated on a scale from 1 to 7, Domain score = (Obtained score – Minimum possible score)/(Maximum possible score – Minimum possible score)