Study Protocol

A protocol for international consensus guideline development on the delineation of radiotherapy target volumes for nasopharyngeal carcinoma after induction chemotherapy

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Background: Induction chemotherapy (ICT) is a therapeutic standard for locally advanced nasopharyngeal carcinoma (NPC). Radiotherapy (RT) target volume delineation protocols and dose level prescriptions vary importantly in published studies. We aim to develop a consensus guideline to harmonize practices in this regard.

Methods: The study consists of the following phases: Consensus Scope Definition by focus group discussion (FGD); Evidence Gap Identification by a scoping review of guidelines and literature reviews; Evidence Review and Synthesis by a systematic review of experimental and observational studies and Drafting of Consensus Statements by FGD; and Consensus Voting by modified Delphi process and FGD. The Task Force consists of radiation oncologists from intermediate- and high-endemicity regions with expertise in the treatment of NPC, evidence review and/or consensus guideline development. The Consensus Panel (CP) will consist of relevant specialists from intermediate- and high-endemicity regions or with expertise in the treatment of NPC. The consensus voting process will entail a presentation and discussion of evidence summaries, followed by 1–3 rounds of voting. Each round will consist of an independent voting using the modified e-Delphi process followed by an *en banc* review and deliberation of the summary of the votes. Up to three rounds will be conducted, after which items for which no consensus was achieved will be indicated thus. The consensus guideline will be reported per the ACCORD guidance document and reviewed externally using the AGREE II checklist.

Discussion: An international consensus guideline on the delineation of RT target volumes and corresponding dose levels in post-induction NPC, and timing and modalities for imaging will help harmonize practices and improve the comparison of reported outcomes.

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Introduction

Induction (or neoadjuvant) chemotherapy (ICT) is currently a therapeutic standard for locally advanced non-metastatic nasopharyngeal carcinomas (NPC) with a high level of evidence (1-3). Several randomized controlled trials, two meta-analyses (4,5) and two systematic reviews of literature (6,7) confirmed the positive impact of adding ICT to concurrent chemoradiation in locally advanced non-metastatic NPC on different survival parameters. Non-endemic NPC is usually treated following the guidelines for endemic NPC although there are no specific trials for the former and the evidence for ICT is less clear (8-11).

Previous delineation consensus guidelines do not accurately specify radiation therapy target volumes and dose levels based on response to ICT (12,13). A phase III randomized trial comparing the delineation of pre-chemotherapy volume with delineation of post-chemotherapy volume showed, with a median follow-up of 98.4 months, comparable survival results between the two groups (overall, progression-free, locoregional recurrence-free, and distant metastasis-free survival) with less xerostomia, decreased hearing and better quality of life in favor of post-chemotherapy volume (14).

The aim of this study is to develop a consensus guideline towards harmonizing practices based on a literature review and expert opinion (through an online survey).

Methods

Study design

The consensus guideline development will be undertaken from September 2023 to April 2024 and will consist of the following phases (*Figure 1*):

(I) Consensus Scope Definition, by focus group discussion (FGD);
(II) Evidence Gap Identification, by a scoping review of published guidelines and reviews on the subject;
(III) Evidence Review and Synthesis, on the identified clinical questions, by a systematic review of experimental studies and observational studies, and Drafting of Consensus Statements, based on the evidence synthesis, by focused group discussion; and
(IV) Consensus Voting, by modified Delphi process and FGD.
(V) Reporting and External Review, using standardized checklists.

Project management, task force committee and panel membership

(I) Project Leader, oversight: Dr. Warren Bacorro.
(II) Project Manager, coordination: Dr. Hela Hammami Turki.
(III) Task Force Chairs: Dr. Jamel Daoud, Dr. Michael Benedict Mejia.
(IV) Committee Chairs:
  (i) Steering: Dr. Melvin L. K. Chua, Dr. Nejla Fourati;
  (ii) Evidence Review: Dr. Ryan Anthony Agas, Dr. Omar Nouri;
  (iii) Conflict of Interest (COI) Review: Dr. Hela Hammami Turki;
  (iv) Methodology: Dr. Warren Bacorro.
(V) Panelists. The composition and membership will be determined once the scope has been finalized, and the clinical questions and consensus statements have been drafted:
  (i) Consensus;
  (ii) External Review.

Review and management of COI

All committee members and potential panelists will be required to submit their updated curriculum vitae (CV) and a complete disclosure using a COI form prior to the initiation of consensus statement development.

Potential COI will include financial, intellectual, or other personal interests that could be perceived by others

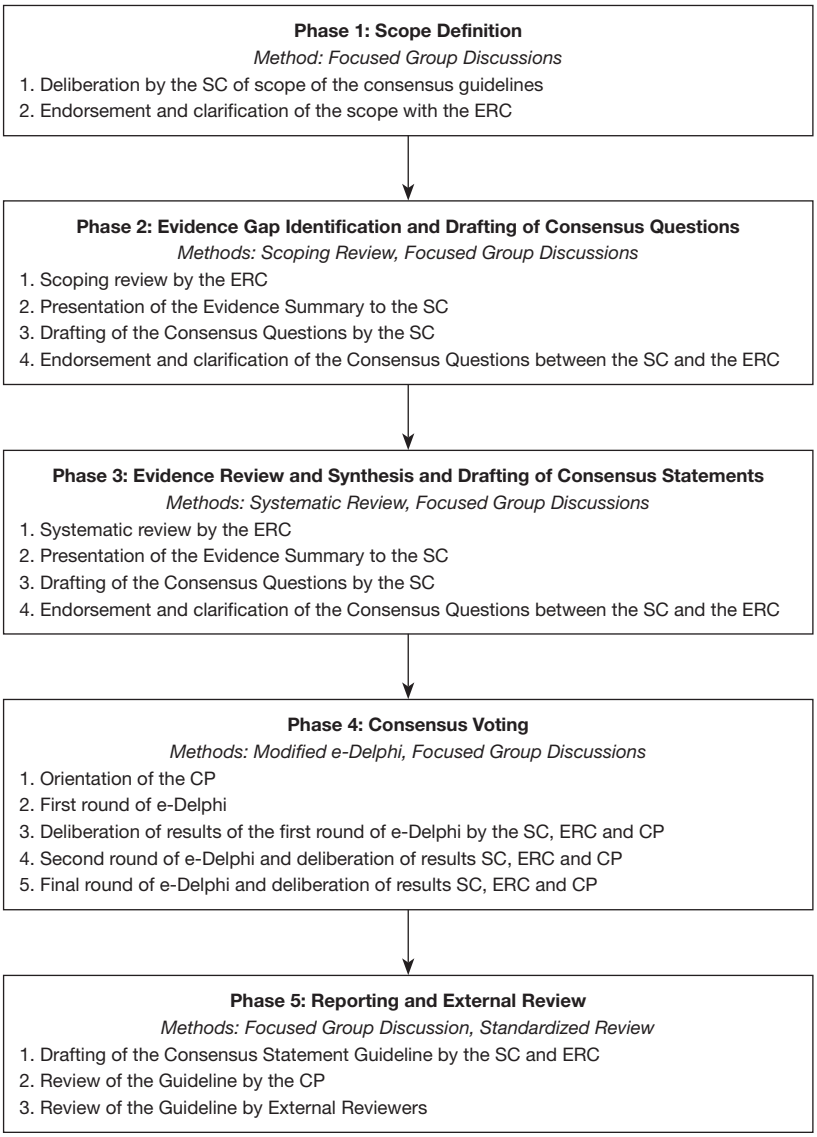

Figure 1 Consensus guideline development process. SC, Steering Committee; ERC, Evidence Review Committee; CP, Consensus Panel.

to influence your judgement on issues addressed by the consensus statement (e.g., use of imaging modalities, chemotherapy). Potential COI will include both personal (primary) and those emerging from immediate family members (secondary) (15). The scope of disclosure will include a four-year period and will include any expected or foreseen relationships or engagements within one year after publication.

The COI Review Committee (COIRC) will consider the disclosure and contributions to the field of the panelists both as individuals and in aggregate to ensure a balanced panel. The following relationships will be generally acceptable: (I) intellectual and without financial benefit; or (II) unrelated to the content are and focus of the clinical question. The following relationships will be considered manageable: (I) significant intellectual COI (may be managed by broadcasting COI during participation in meetings); and (II) intellectual COI with financial COI (may be managed by allowing to discuss without voting power). The COIRC may request for further details from the committee member or panelist as necessary.

Based on the review, the committee member or panelist may be (I) allowed to perform designated function without constraints; (II) allowed to perform designated function but

will need to broadcast and may be prohibited to discuss or vote whenever necessary; (III) allowed to discuss but cannot vote; or (IV) disallowed from any participation (15).

The COIRC will communicate to each committee member or panelist the final decision letter including the management plan and the justification. Any appeals will be considered by the COIRC. All panelists will agree to adhere to any COI management terms and will disclose any new potential COI once identified. Each panel meeting will begin with a verbal reminder of this policy. All potential COIs and management terms and the COI review and management process will be published as part of the final article for transparency.

Phase 1: Consensus Scope Definition

The Steering Committee (SC) will define the scope of the consensus statement after the first literature review (guidelines, systematic reviews, narrative reviews).

The scope will include, but may not be limited to, the following:

(I) Optimal timing for post-induction radiotherapy (RT);
(II) Optimal imaging modality pre- and post-induction for RT target delineation;
(III) RT target volume delineation: high-risk, intermediate-risk, low-risk; and
(IV) RT dose prescription and fractionation.

The SC will finalize the scope of the guidelines after the scoping review. The SC will then develop and rank clinical questions and draft consensus statements, which will guide the systematic review. The SC will finalize the questions and consensus statements after the systematic review.

Phase 2: Evidence Gap Identification

The Evidence Review Committee (ERC) will conduct a scoping review of guidelines, systematic reviews, and narrative reviews to map the current scope of discourse on the topics encompassed by the consensus scope and identify evidence gaps.

The scoping review will entail a systematic search on at least two electronic scientific databases. The search strategy will employ both controlled vocabulary and free-text search terms and will be peer-reviewed. The ERC will present the outcomes of the scoping review to the SC in a focused group discussion, towards drafting clinical questions.

Phase 3: Evidence Review and Synthesis and Drafting of Consensus Statements

The ERC will conduct a systematic review of experimental studies (or observational studies if experimental studies are lacking) and apprise and synthesize evidence on the clinical questions.

The systematic review will entail a systematic search on at least two electronic scientific databases (PubMed, ScienceDirect). The search strategy will employ both controlled vocabulary and free-text search terms and will be peer-reviewed. The screening, appraisal, and/or data extraction will be performed by at least a designated primary reviewer and a secondary (peer) reviewer. The review procedures will adhere to the Cochrane guidelines for systematic reviews (16). Critical appraisal and assessment for risk of bias will be done using the McMaster Critical Review Forms.

The ERC will present to the SC the evidence synthesis in a focused group discussion towards drafting a consensus statement/s corresponding to each clinical question.

Phase 4: Consensus Voting

The composition and membership of the Consensus Panel (CP) will be determined once the SC has finalized the clinical questions. At the minimum, the CP will include 13 radiation oncologists, three medical physicists, three medical oncologists, three radiologists, and three nuclear medicine specialists. An international representation will be ensured, including centers in high- and intermediate-endemicity regions, and/or with extensive and relevant experience on the subject.

A modified e-Delphi method will be employed for several rounds until consensus is reached. Each clinical question will be answerable by "strongly agree (SA)", "agree (A)", "disagree (D)", and "strongly disagree (SD)". Each round of e-Delphi will be followed by a conference call to discuss results. Consensus will have been reached if >50% voted to agree (SA + A) or disagree (SD + D). The vote will be uniform, if it constitutes 100%; strong if ≥85%; moderate if 75–84%; or weak if <75% (12). If despite the third and final conference call, the vote remains equally split (50/50), "No consensus reached" will be declared.

Phase 5: consensus statement Reporting and External Review

The consensus statement will be reported according to the

ACCORD (Accurate Consensus Reporting Document) guidance (17,18), pending publication of the ACCORD guidelines.

The consensus statement will be independently reviewed by two radiation oncologists, and one each of the following: medical physicist, medical oncologist, radiologist, and nuclear medicine specialist. The membership will be determined once the consensus development process has been completed and the final version has been drafted.

The AGREE II checklist for critical appraisal of clinical practice guidelines will be used (19). The ERP members will review the consensus statement independently. The results of the external review will be reported in the consensus statement, either in the main manuscript or as a supplementary file.

Discussion

The sources for variation in the delineation of RT target volumes may arise from any of the following: timing and modality of post-induction pre-RT imaging, decision to treat initial disease extent and to what dose (14), different scenarios of post-induction response to chemotherapy, and different extents of initial disease involvement (mucosa, muscle, nodal, extranodal, bone, perineural, intracranial). Systematic reviews and critical appraisal of literature on imaging and delineation protocols, survival, disease control, and toxicity outcomes, patterns of failure, and prognostic factors for locoregional failure and toxicity will be necessary.

For applicability, a consensus will need to be made as to what studies will be included in the evidence review, in terms of the neoadjuvant chemotherapy regimen used. While taxane, platinum and 5-fluorouracil combination has been demonstrated to be superior to platin and 5-fluorouracil combination, the associated toxicity may limit adoption of the former in limited-resource settings. Gemcitabine-platinum combination has been shown to improve survival and may be associated with better cost and toxicity profile (7,20).

An international consensus guideline on the delineation of RT target volumes and corresponding dose levels in post-induction NPC, as well as timing and modalities for imaging will help harmonize practices and allow for better comparison of outcomes in clinical trials and observational studies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://anpc.amegroups.com/article/view/10.21037/anpc-23-1/coif). W.B. reports registering a nasopharyngeal brachytherapy applicator design (Philippine IPO 12018000010) and receiving sponsorship from Elekta and Bebig for USTH-BCI Head-and-Neck Brachytherapy Workshop. M.L.K.C. serves as the Editor-in-Chief of *Annals of Nasopharynx Cancer*. M.L.K.C. reports grants or contracts from Ferring, personal fees from Astellas, Bayer, MSD, Janssen, Pfizer, BeiGene, Varian, IQVIA, Telix Pharmaceuticals, personal fees and non-financial support from AstraZeneca, non-financial support from Decipher Biosciences, non-financial support from MedLever, consults for immunoSCAPE Inc., and is a co-inventor of the patent of a High Sensitivity Lateral Flow Immunoassay For Detection of Analyte in Sample (10202107837T), Singapore and serves on the Board of Directors of Digital Life Line Pte Ltd. that owns the licensing agreement of the patent, and hold stock on Digital Life Line, outside the submitted work. M.B.M. serves as an unpaid editorial board member from August 2023 to July 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study will not entail human participants or use of human data and does not require ethical review or informed consent.

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