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Original article

International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma

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ABSTRACT

Purpose: Target delineation in nasopharyngeal carcinoma (NPC) often proves challenging because of the notoriously narrow therapeutic margin. High doses are needed to achieve optimal levels of tumour control, and dosimetric inadequacy remains one of the most important independent factors affecting treatment outcome.

Method: A review of the available literature addressing the natural behaviour of NPC and correlation between clinical and pathological aspects of the disease was conducted. Existing international guidelines as well as published protocols specified by clinical trials on contouring of clinical target volumes (CTV) were compared. This information was then summarized into a preliminary draft guideline which was then circulated to international experts in the field for exchange of opinions and subsequent voting on areas with the greatest controversies.

Results: Common areas of uncertainty and variation in practices among experts experienced in radiation therapy for NPC were elucidated. Iterative revisions were made based on extensive discussion and final voting on controversial areas by the expert panel, to formulate the recommendations on contouring of CTV based on optimal geometric expansion and anatomical editing for those structures with substantial risk of microscopic infiltration.

Conclusion: Through this comprehensive review of available evidence and best practices at major institutions, as well as interactive exchange of vast experience by international experts, this set of consensus guidelines has been developed to provide a practical reference for appropriate contouring to ensure optimal target coverage. However, the final decision on the treatment volumes should be based on full consideration of individual patients' factors and facilities of an individual centre (including the quality of imaging methods and the precision of treatment delivery).

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Introduction

Radiation therapy (RT) is the primary treatment modality for nasopharyngeal carcinoma (NPC). Target delineation in NPC often proves challenging because of the notoriously narrow therapeutic margin. High doses are needed to achieve optimal levels of tumour control, despite the apparent radio-sensitivity of the tumour in many patients. Even in the contemporary era of intensity-modulated radiotherapy (IMRT) with extensive use of concurrent chemotherapy, dosimetric inadequacy remains one of the most important independent factors affecting treatment outcome. A study by Ng et al. showed that the 5-year local failure-free rate dropped to 54% if more than 3 cc volume within the gross primary tumour was under-dosed to below 66.5 Gy, compared with 90% in patients with smaller under-dosed volumes ($p < 0.001$) [1].

With the anatomical proximity of critical organs-at-risk (OARs), the importance of appropriate contouring to attain optimal balance between the risk of tumour recurrence due to marginal miss and the risk of serious late damage cannot be over-emphasized. The first fundamental step is accurate delineation of the Gross Tumour Volume (GTV) for individual patients based on the best available investigation methods. With the well-known highly infiltrative behaviour of NPC, especially the common non-keratinizing subtype, the next critical step is proper delineation of the clinical target volume (CTV) to cover the sites at relatively high risk of microscopic involvement. However, there are marked variations in philosophy and practice among clinicians [2].

The Danish national guidelines for delineation of CTV for head and neck squamous cell carcinoma (2013) [3] proposed the concept of isocentric "5 + 5 mm" geometric expansion of the primary tumour Gross Tumour Volume (GTVp), with corrections for natural anatomic boundaries such as bone or air cavities [4]. The principle is to deliver the full therapeutic dose to the CTV1 that covers at least the GTV + 5 mm margin, and a lower (prophylactic or intermediate) dose to the CTV2 that covers CTV1 + an additional 5 mm rim of tissue. The use of these guidelines has led to much more homogeneous target volume delineation among centres, as noted in data collected by Hansen et al. [5]. However, as the editing was mainly proposed for natural boundaries only, it is expected that the Danish national guidelines result in the inclusion of more non-target tissues in the tumour CTV (CTVp) than should ideally be included. Further refinement has recently been initiated by Vincent Grégoire and Cai Grau, to comprehensively review the Danish national guidelines and to edit for each anatomic location within the larynx, hypopharynx, oropharynx and oral cavity; and specifically, for each T-category within the TNM staging classification by incorporating knowledge of anatomy and the patterns of spread of disease into the geometric CTV delineation concept [6].

The key objective of this proposed guideline is to develop recommendations on delineation of CTV specific to NPC that will provide clinicians with a practical reference on treatment principles, with a fundamental goal of providing a reference for appropriate contouring to ensure adequate tumour coverage. This document is based on consensus built by review of available evidence, comparison of published guidelines [2,7–9] and detailed consideration of opinions and successive rounds of consensus by international experts experienced in the treatment of NPC. This guideline represents the concerted efforts of key oncologists from Asia (China, Hong Kong, Korea, Singapore, Taiwan), Australia, North America (Canada, United States), Saudi Arabia and Europe (Belgium, Denmark, France, The Netherlands, Turkey, United Kingdom). The guideline should be applicable for all histological subtypes of NPC.

General description of the procedures for acquisition of planning CT and delineation of GTV

Acquisition of the planning CT

The patient should typically lie in the supine position on the flat table-top of the simulation CT scanner with the head and neck immobilized in a neutral neck position by a reproducible immobilization device, most commonly a 4–5 fixation point thermoplastic mask covering from skull vertex to shoulder [10].

Thin CT sections (preferably 2 mm thickness) should be acquired typically from vertex to 2 cm below the sternoclavicular joints. We suggest scanning from the vertex in order to include the entire brain, to facilitate dose calculations. As parts of the brain will receive an appreciable dose of radiation which can result in significant toxicity, this will enable future examination of any dose–effect relationships for different endpoints within the central nervous system (CNS) anatomical substructures.

CT acquisition should ideally be done with intravenous iodine contrast enhancement. In cases where intravenous contrast medium is contraindicated, such as allergies to contrast medium or renal insufficiency, all measures should be taken to ensure the availability of optimal image sets for planning, e.g. fusion with M RI ± FDG-PET images.

Delineation of the primary tumour GTV

Accurate delineation of the primary tumour GTV (GTVp) requires the synthesis of clinical and imaging data collected during the work-up procedure.

This includes:

- a detailed clinical examination of the anterior nasal space, nasopharynx, and oral cavity, with fiberoptic nasopharyngoscopy with a detailed description of the tumour extension and infiltration,
- a diagnostic contrast-enhanced MRI performed within 2–3 weeks of RT planning and fused with the planning CT. Ideally, the MRI should be acquired in the treatment position with the use of an MRI-compatible radiation therapy immobilization device,
- close collaboration with diagnostic radiologists sub-specializing in head and neck oncology, is highly encouraged for clarification of anatomy and disease extensions,
- additional information from PET/CT images may be useful, especially for advanced cases. PET volumes should preferably be reconstructed using user-independent segmentation algorithms [11]. Furthermore, window and contrast level adjustments can drastically alter the target volume, thus the PET/CT images may be helpful to identify small lymph node (LN) metastases that may have been missed on CT or MRI. However, PET/CT should serve only as a guide, as the lack of spatial resolution as well as the partial volume effect results in insufficient accuracy for target volume delineation.

Delineation of the primary tumour CTV

Patterns of spread

Nasopharyngeal carcinomas tend to arise from the fossa of Rosenmüller, spreading submucosally with early infiltration of the palatal muscles within the parapharyngeal space. Due to its highly infiltrative nature, it spreads easily through areas of lesser resistance within the pharyngobasilar fascia, and tends to infiltrate along neural pathways. Dubrulle et al. [12] described the routes of

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