



Nasopharyngeal carcinoma contouring guidelines—the first step in a thousand mile journey

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“The journey of a thousand miles begins with one step.”—Lao Tzu (NOT Confucius).

Contouring consensus guidelines for head and neck carcinomas have been available as a useful tool for the radiation oncologist from various known experts and cooperative groups around the globe (1). However, nasopharyngeal carcinoma (NPC) is a disease unique in its epidemiology and behavior, necessitating separate guidelines for this distinctive head and neck malignancy.

Lee and her co-authors made a valiant first attempt in reaching and publishing a consensus amongst regional and global experts in radiation oncology regarding the most appropriate volumes and dose levels for the disease (2). Notable in the publication is substantial disagreement amongst the experts on various aspects of volume and dose prescription. The disagreement amongst the expert panel is not unexpected as the contouring and dose prescription protocols in their respective centres have shown impressive numbers in terms of survival, control and risks for severe toxicity.

At our institute, like in most other Asian centers, we include the entire nasopharynx in the high-risk CTV (GR-CTV, or CTVp1). The consensus defines the nasopharynx as just the mucosa and not including the pre-vertebral muscles, unless involved. Inclusion of this entire structure should not add toxicity and should be more in-keeping with the definition of HR-CTV. Even in the absence of evidence of abnormalities on MRI, the entire nasopharynx is in theory at high-risk of occult disease (field cancerization) as is the case for cervical cancer, for which the entire cervix is considered part

of the HR-CTV. Furthermore, similar to the junction line that exists in the cervix, there exists an intermediate pseudostratified cuboidal type that is a transition between the pseudostratified columnar epithelium and the squamous epithelium. This intermediate epithelium is most susceptible to carcinogenesis, thus the propensity of NPC to grow in the lateral walls, posterior wall and anterior walls, in that order, corresponding to the predominance of this intermediate epithelium (3). The caudal border should theoretically cover this transition zone, which may vary among individuals. The C1 or level of the soft palate seems reasonable and coincidentally, this is included within the usual prescription isodose volume in intracavitary brachytherapy (ICBT) (4) which is given as a boost in some Asian centers. Less margin is thus necessary anteriorly and should enable us to spare the soft palate.

The 5+5 mm expansion as proposed by the DAHANCA guidelines and also basically agreed upon by other trial groups (5,6) may not be unreasonable for the intermediate-risk CTV (IR-CTV, or CTVp2), but we have to agree that NPC is biologically different from other HNSCC and may need some refinements in redefining the extent which requires a higher radiation dose. In this era of personalisation of treatment and high tech “dose-painting” and adaptive radiotherapy (RT), more accurate identification and delineation of areas at high risk of local failure is brought more to the forefront. Also, the predisposition for NPC for perineural spread as well as the exquisite radiosensitivity of the tumor makes it necessary for radiation oncologists to think outside the “5+5” paradigm when treating NPC or to find suitable

adaptations for the disease.

Local failure is either marginal or within the high-dose region. The objective of standardisation of target delineation is to decrease the incidence of marginal and geographic misses and hopefully, the evolution of these guidelines will allow for a more thorough understanding of the patterns of spread of NPC. However, a good number of failures still occur within the high-dose region. It is important to likewise look at certain prognostic indices and biomarkers to define a population of NPC patients who may benefit from trials of dose escalation. A paper published at the *JCO* may provide the initial clues to radioresistance of some patients with NPC (7). In a similar light, it is imperative to dichotomize in future studies the “true failures” which herald truly resistant disease and differentiate them from the marginal failures, which may be a result of inadequate tumor coverage in either the CTVp1 or the CTVp2. The former should occur in the high dose region and should have received as little treatment breaks as possible and with an acceptable cumulative cisplatin dose. The crux of the issue is how little a treatment break can be labeled “reasonable” and what is the “acceptable” cumulative level of cisplatin. Our centre implements keeping overall treatment time for radiotherapy at a maximum of 7.5 (1 week maximum cumulative treatment break) and attempts to achieve 200 mg/m² of concurrent cisplatin in all patients. Induction chemotherapy is only given upon consensus by the NPC tumor board that the risk of distant metastasis warrants the delivery of ICT.

There also appears to be no recommendations for low-risk CTV (LR-CTV) such as coverage above the skull base as the most superior extent of the recommendations mention up to the foramina ovale, rotundum, lacerum and petrous tip. Too stringent coverage criteria may present a risk for intracranial failure via the perineural route. Perhaps the traditional volumes covered in the seminal work by Ho (8) wherein the fields covered potential intracranial extension by bringing the parallel opposed fields 10–15 mm above the sella turcica and coning down after 54–60 Gy. Indeed, our series show penumbral failures at or above the skull base, indicating the presence of subclinical perineural spread despite the absence of intracranial spread in pre-RT evaluations (*Figure 1*). The patients with the latter failures received their definitive treatment in low-volume, community centers, albeit

following standard treatment guidelines, commonly the National Comprehensive Cancer Network guidelines.

Indeed, even in the era of intensity-modulated radiotherapy and chemoradiation (CRT) with excellent local control rates (up to 85.8% overall 8-year failure-free survival; T1: 91.7%, T2: 88.2%, T3: 87.2%; T4, 71.6%) have been achieved (9). NPC recurrences within high-dose regions occur, indicating radioresistance. The benefit of dose escalation has been demonstrated even in the era of CRT (10) and some centers in Asia continue to give ICBT boost in order to dose-escalate in AJCC 7 T1–T2 disease (11,12). The guideline is reassuring for centers that do ICBT boost, in that the CTVp1 and CTVp2 should be well-covered by the 350 and 140 cGy isodose volumes if ICBT is given in 350 cGy fractions twice-daily (see photo) (4).

Finally, there have been publications showing that outcomes in head and neck cancers appear to be better when these patients are treated in higher volume academic centers by high volume, specialists (13,14). It appears that while the expert panels and the institutions they treat in meet the criteria separately mentioned by Corry and David, the outcomes would intuitively be different amongst different institutions with different levels of subspecialist expertise, even if the contouring and prescription guidelines were followed to the letter where patients treated in high volume centers by high volume specialists may have better outcomes than those treated in lower volume centers by general radiation oncologists. These findings remind us that while these guidelines serve to standardize target delineation and dose prescription, good outcomes result from sound clinical judgment, good and collaborative clinical practice. Radiation oncologists will have to work collaboratively with radiologists for accurate GTV delineation, with medical physicists and radiation technologists towards accurate treatment delivery, and with the medical oncologist and the patient himself, for proper management of treatment toxicity and thus compliance.

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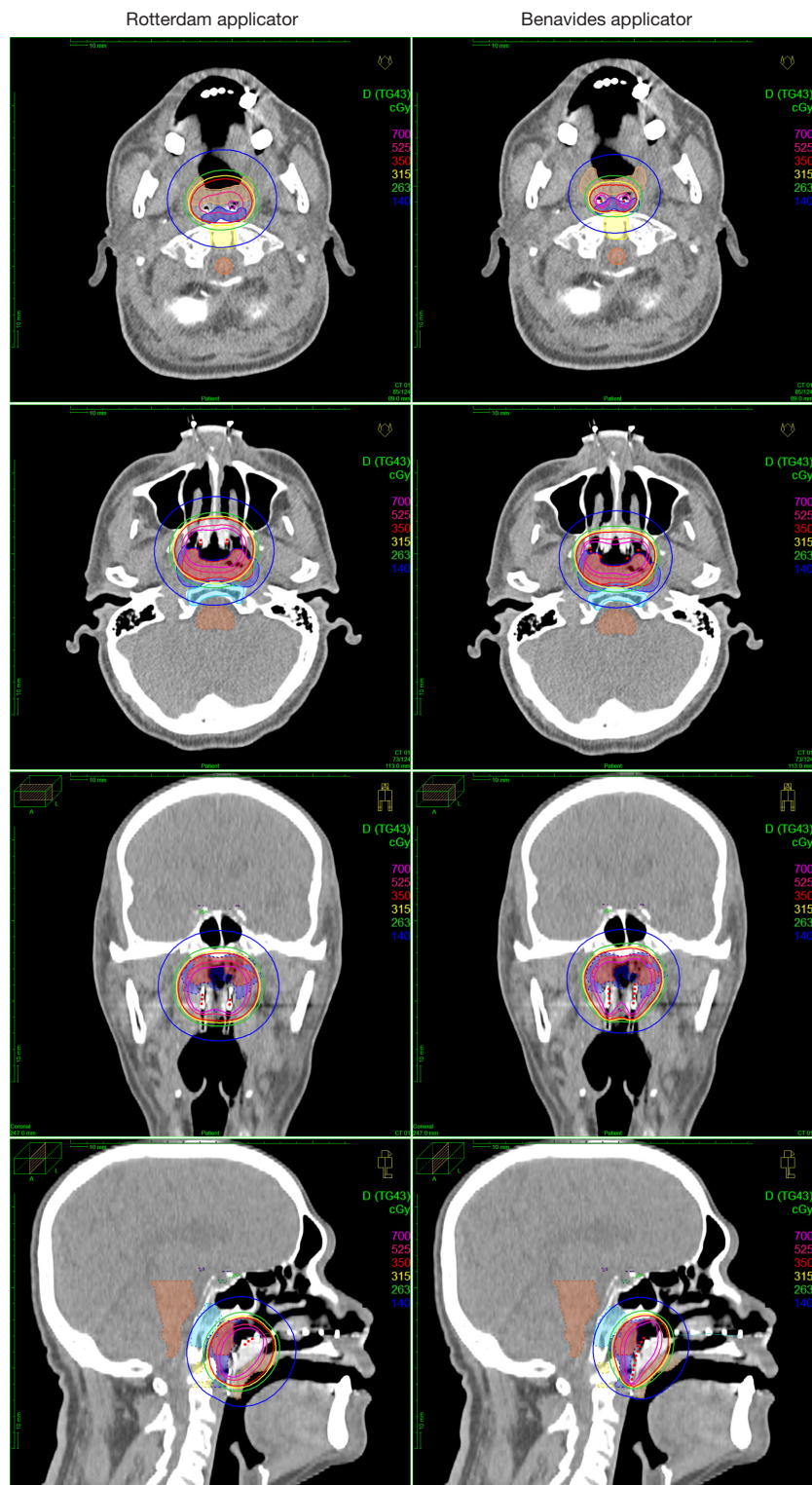


Figure 1 Comparison of soft palate sparing and isodose profiles of the Rotterdam and proposed Benavides applicator in a T2 tumor in representative axial, sagittal, and coronal planes. Volumes: The HR-CTV is in red; IR-CTV, dark blue; brainstem, orange; clivus, light blue; atlanto-axial joint, yellow; and soft palate, beige. Isodose: The red line represents the prescription dose, 350 cGy.

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