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CTV Guidance for Head and Neck Cancers

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It is widely accepted that highly conformal radiation therapy techniques, most notably intensity-modulated radiation therapy (IMRT), have revolutionized treatment of head and neck cancers (HNC). The ability to sculpt dose to gross tumor volume (GTV) with margin to create clinical target volumes (CTVs) has resulted in better sparing of normal tissues, significantly reducing toxicity of radiation therapy. As compared to the more morbid severe xerostomia, fibrosis, dysphagia, and risk of permanent feeding tube dependence of conventional radiation therapy, modern IMRT engenders significantly less long-term toxicity and consequent improved quality of life (1). Randomized trials of IMRT compared to conventional radiation therapy have demonstrated improved parotid function and xerostomia-related quality of life (2). In addition to toxicity measures, there is also suggestion of a survival benefit for patients treated with IMRT (3). Few will argue that IMRT has not caused a seismic shift in the outcomes of patients treated for HNC.

Despite headlines of the improvement with “conformal” radiation therapy like IMRT, it is clear that one person’s target volume is not everyone’s target volume. Hong and colleagues documented variations among 20 institutions with HNC IMRT expertise asked to contour an identical case; “substantial heterogeneity” was identified in both treatment regimen (use of chemotherapy, dose) and target delineation (unilateral vs. bilateral, expansions, anatomic boundaries) (4). The extent of interobserver variability has been studied, with the suggestion that it is the “largest uncertainty” in treatment planning, risking a “systematic error in dose delivery” (5). As such, there is urgency to streamline and harmonize contour delineation within the field.

In Lee et al. and Gregoire et al., recently published in *Radiotherapy and Oncology*, international HNC thought leaders provide detailed guidance on delineation of GTV and CTVs for cancers of the nasopharynx and the larynx, hypopharynx, oropharynx, and oral cavity, respectively. In both articles, there are consensus guidelines on CTV contouring, with an attempt to discuss both the basic geometric expansions recommended by DAHANCA

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(“5+5”) and more traditional anatomic expansions that emerged as a result of historic conventional field boundaries and knowledge of patterns of failure and pathways of disease spread. As such, these meaningful and practical guidelines on contouring have the potential to standardize target delineation for HNC moving forward; however, details of the articles do lend some important caveats.

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In Lee et al.’s discussion of nasopharyngeal contouring, the authors rely on anatomic delineation of at-risk areas, noting that geometric expansions are inherently limited due to the lack of pathologic data. This is a vitally important point for nasopharyngeal cancer; with a dearth of pathologic data, the authors cull decades of clinical practice into well-explained and documented recommendations. By citing levels of evidence, they allow for various levels of comfort in the delineation, with more generous and less generous CTVs as a result, based on clinical preference. While this allows for personalization of contouring by each provider for each case, it also does serve to allow continuation of greater variability that has been plaguing the field. In a thoughtful discussion, the authors also examine controversy over contouring following induction chemotherapy. With a recognized lack of data, the authors recommend coverage of the full pre-chemotherapy extent of disease, consistent with the approach in the majority of HNC; however, they note that chemotherapy response (and geometric reduction) may be considered for volumes that otherwise would compromise critical organs at risk. With a growing literature suggesting a benefit to induction chemotherapy for nasopharyngeal carcinoma, this is especially timely.

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In Gregoire et al., a multi-national group of HNC experts walk through careful and specific recommendations for CTV delineation for cancers of the larynx, hypopharynx, oropharynx, and oral cavity. These guidelines emerged from consensus discussions based on the 2013 Danish national guidelines that recommend a high-dose volume ($CTV1 = GTV + 5mm$) and intermediate-dose volume ($CTV2 = CTV1 + 5mm$), now edited based on anatomic boundaries. The authors note a clear recommendation for work-up of the primary tumor, including a fiberoptic nasopharyngolaryngoscopy (or photographs if not feasible to do one personally), an examination under anesthesia with drawings or photographs, a diagnostic CT or MRI within 3–4 weeks before simulation, and FDG-PET/CT for locally advanced tumors. Of note, the large variation in quality of diagnostic imaging and interpretation, as well as variations in technologic capabilities (e.g. deformable registration) at low vs. high-volume academic centers may bias delineation of a target from the beginning. The authors move on to provide well-illustrated examples of appropriate contouring for each site and T-stage.

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The well-explained CTVs of Gregoire et al. may strike a general audience as limited. The authors note that the “5 + 5” approach has been implemented successfully by DAHANCA (6) with resultant decrease in variation between centers; however, they do not cite data on tumor outcomes with this technique. The risk for such minimal expansions is that rarer subsites, such as soft palate or hypopharynx, may not have significant numbers and adequate follow-up since 2013 to truly capture rates of recurrence. Furthermore, there is some risk in the suggestion that CTV-P2 is not necessary for “well-defined” T1 tumors, especially for potentially aggressive subsites such as hypopharynx, when the surgical series note lymphatic spread of 20 – 30 mm (Article REF #36). The authors admit that surgical data can be used to

justify larger margins in some cases, but desire to spare organs at risk also needs to be prioritized.

Practically speaking, integration of the 5 + 5 approach with adjustment based on anatomic landmarks may be challenging for clinicians who do not routinely see a high volume of HNC patients. Prior work has noted that patients treated with IMRT by physicians at high-volume centers had improved outcomes compared to those treated by low-volume centers; this difference was not seen for conventional treatments (7). This finding could be applied either way with regard to this paper; on one hand, it may suggest that the detailed contouring recommendations are now more easily integrated into practice for low-volume practitioners, raising the bar, but on the other hand, it may suggest that these limited margins, with nuanced adjustments based on obscure anatomic findings, simply exacerbate the issue and lead to a widened gap in outcomes.

Furthermore, Gregoire et al. note that the recommendations only account for GTV expansions to create high-risk (CTV-P1) and intermediate-risk (CTV-P2) volumes. They note specifically that these “do not account for organ motion and/or set-up uncertainty” and recommend that centers add ITV/PTV margin to account for immobilization techniques, imaging techniques, and motion based on their local data. They move on to suggest that a 3–5 mm PTV margin has been proposed. While this is a guideline integrated into many multi-institutional randomized trials of IMRT, this largely relies on larger CTV margins, which do integrate more anatomic coverage and adjustments due to some internal organ motion (not just set-up uncertainty). Prior work has established that the larynx may have posterior displacement of up to 17 mm (8) and superior displacement of up to 16.1 mm during swallowing (9). This may have profound impact in coverage, not accounted for with modest expansions and limited PTVs.

While many practitioners may express concern about the margins seeming limited (as above), that may simply reflect ongoing bias. In Jager et al., the authors document that median GTVs were significantly larger than tumor volume on pathology (10). Hence, current practices of HNC IMRT, largely influenced by the prior anatomic landmarks of conventional treatment, may simply be anachronistic in this era. Fundamentally, improved imaging modalities, the opportunity for more conformal therapy (through advancements in treatment planning and new modalities, such as proton therapy), allow us to treat more conformally. The first step in that is creating more limited but rationally designed targets. Time will tell whether or not the ability to elucidate tumor more clearly, create more limited CTVs, and deliver more conformal therapy engenders better outcomes with regard to cancer control and limited toxicity or whether it demonstrates a greater risk for recurrence due to underappreciation of microscopic disease or uncontrolled motion leading to underdosing of the tumor. Additionally, the proposed “5+5, minus uninvolved anatomy” reintroduces some heterogeneity that groups like DAHANCA have been seeking to reduce. When available, HNC practitioners will continue to incorporate MRI and PET imaging findings into their GTV designs, adding to heterogeneity. In the future, radiomics and machine-learning may help us incorporate CT, MRI, and functional imaging characteristics into a more objective GTV contour.

These two papers are thoughtful, well-organized, and well-referenced treatises on contouring primary tumor CTVs for HNC. They will serve as outstanding education materials and guidelines for clinical work for decades to come. That said, practitioners should assess their comfort level with the quality of imaging at their center, their command of CT- and MR-based anatomic imaging, and the quality of the available endoscopic information, and adjust their expansions accordingly to ensure that they can feel confident that the treatment they are delivering is the best for their individual patients, with risk for recurrence weighed carefully with risk of toxicity.

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