Management of the neck in nasopharyngeal carcinoma—time for a radical change?

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Nasopharyngeal carcinoma (NPC) is a unique cancer of the head and neck, with a characteristic demographic and geographical distribution (1). In the endemic regions e.g., Southeast Asia, Southern China, and North Africa, NPC is invariably associated with the Epstein-Barr virus (EBV) infection, which has been implicated as an integral pathogenetic pathway of this cancer (2,3). Whether these viral and epidemiological associations account for the unique presentations of NPC patients e.g., extreme local symptoms of cranial nerve palsies or bulky nodal disease, are unclear, but nodal metastases are a common phenomenon in NPC, even for small primary T1-2 tumours (4,5). A retrospective analysis of 5,037 NPC patients treated over the period of 1976 to 1985 revealed that clinically node-negative patients who had received prophylactic nodal irradiation experienced significantly lower nodal relapses compared to patients without treatment to the neck (11% *vs.* 40%) (6). Furthermore, despite successful salvage of the neck, patients with nodal relapse subsequently experienced a higher distant metastatic rate than those without relapse (21% *vs.* 6%) (6). Consequently, prophylactic whole neck irradiation (WNI) was mandated in the treatment of patients with NPC, even for those with node-negative disease. However, detection of nodal involvement during that era was based on clinical palpation. With advances in imaging modalities such as magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), the sensitivity and specificity of detection of nodal metastasis have substantially improved, thus rendering under-staging uncommon (7,8).

A key feature of nodal metastasis in NPC is the orderly pattern of spread. The first echelon nodal stations are the retropharyngeal and upper cervical level II lymph nodes, followed by levels III and Va, then levels IV and Vb/c, as the second and third echelon routes of spread, respectively. Two retrospective studies that mapped the lymph node metastases for 786 and 101 NPC patients had reported that skipped metastases were rare in NPC, occurring at an incidence of less than 10% (9,10). These observations raise the possibility that the clinical target volume (CTV) for prophylactic neck irradiation could be more selective. On this note, 2 prospective studies were published in 2013 to address this question, albeit in different patient populations—in both studies, the de-escalation strategy entailed omission of irradiation of the levels IV and Vb/c lymph node stations (11,12). The first trial recruited 301 patients with node-negative NPC staged by MRI, and randomised patients to upper neck irradiation (UNI) or

WNI (11). They reported no nodal relapse, with comparable 3-year overall survival (OS) between the treatment groups. The second study was a single-arm prospective phase 2 study that investigated the safety of UNI in 212 patients with N0-1 NPC (12). Patients harbouring retropharyngeal lymph node involvement with or without cervical lymph node metastasis were eligible, regardless of T-category. Patients were prescribed 60–66 Gy over 30 fractions to the involved nodes, while prophylactic UNI was delivered to 54 Gy over 30 fractions. They reported a nodal relapse rate of 3.3% (7/212). Collectively, both trials suggested that UNI was safe, and yielded excellent regional control rates. This information was taken into consideration when the international consensus guideline on contouring of CTV was developed in 2017. Most experts would extend the coverage to one level beyond that with grossly involved lymph nodes. There was high consensus (95%) to cover levels IV and Vb only if there are any involved cervical lymph nodes (excluding retropharyngeal lymph nodes) (13).

In this present study, Tang *et al.* (14) reported their phase 3 randomised trial of 446 patients with N0-1 NPC who were randomised at a 1:1 ratio either to WNI or UNI. The patients were staged by MRI; in addition to 89 (20%) patients with no detectable lymph nodes and 120 (27%) patients with retropharyngeal nodes, they have further included 237 (53%) patients with N1 cervical lymph nodes. Importantly, this was a non-inferiority trial, whereby the investigators permitted an 8.0% non-inferiority margin for their primary endpoint of 3-year regional relapse-free survival (RRFS). Based on a projection of 97% 3-year RRFS for the WNI group, the investigators estimated a sample size of 434 that would have provided an 80% power, accounting for a 5% dropout rate. Secondary endpoints were OS, distant metastasis-free survival (DMFS), local relapse-free survival (LRFS), treatment-related adverse events (TRAEs), and quality of life (QOL) outcomes. In terms of treatment, patients with stage II-IVA NPC were recommended cisplatin-based chemoradiotherapy (CCRT) or induction chemotherapy (IC) followed by CCRT, which was recommended at the discretion of the treating physician. Of note, 82% (367/446) of the overall cohort underwent CCRT, and among them, 27% (122/446) received IC. For their primary endpoint of 3-year RRFS, the investigators found that UNI was non-inferior to WNI; 3-year RRFS was 97.7% for UNI compared with 96.3% for WNI, corresponding to a difference of –1.4%, with a 95% confidence upper limit of 1.8% in the intention-to-treat cohort. Likewise, a comparable magnitude of benefit was observed in the per-protocol population. Finally, OS, DMFS and LRFS rates were comparable between the treatment groups.

For any studies on treatment de-escalation, it is imperative that outcome measures include assessments of TRAEs and QOL, given that the overarching goal of less treatment is to yield benefits in these clinical domains. With the omission of radiation to the lower neck, one should expect reductions of delayed radiation-induced hypothyroidism, dysphagia, and dermatitis/skin tissue damage (15). In this trial, with a median follow-up of 53 months, patients who received UNI experienced significantly fewer delayed TRAEs compared with those who underwent WNI (29% *vs.* 39% for hypothyroidism; 17% *vs.* 32% for dysphagia; 37% *vs.* 64% for skin/soft tissue damage), although no difference was observed for acute toxicities, and most late toxicities were grade 1–2 only in terms of severity. QOL outcomes were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Core 30 items (QLQ-C30) and Quality-of-Life Head and Neck 35 items (QLQ-H&N35) questionnaires at baseline and 3 years post-intensity modulated radiation therapy, with a change in QOL score of at least 10-points defined as clinically meaningful. Consistent with the reduction of delayed TRAEs, UNI patients experienced better QOL scores for global health status (mean change of 5.4), emotional functioning (mean change of 5.3), fatigue (mean change of –5.0), and swallowing (mean change of –10.1) compared with patients in the WNI group; note however that only the delta in swallowing scores met the 10-point meaningful difference. Nonetheless, given the excellent survival rates for NPC, a more clinically meaningful benefit with UNI may be observed with longer follow-up.

Before we take a closer scrutiny of the study results, we must first congratulate the investigators for successfully completing this randomised phase III trial, which now adds to the published evidence by providing us with high-quality data supporting the benefits of sparing the lower neck from radiation in patients with N0-1 NPC. Nonetheless, there are several caveats regarding patient selection, maturity of the results, and statistical design that are important to bring to attention:

- *Heterogeneity of patient population:* it is noteworthy that the study cohort was clinically heterogeneous, comprising of 22% (96/446) TNM-stage I-II and 78% (350/446) TNM-stage III-IV patients by AJCC/UICC TNM 7th edition classification.

In terms of nodal involvement, 20% (89/446) were node-negative, 27% (120/446) had only retropharyngeal node involvement, and 53% (237/446) had cervical lymph node involvement. As approximately half of the trial cohort had N1 disease, it would be interesting to dissect the outcomes for patients within this group, whether they had multiple or single cervical lymph node involvement, or if the cervical nodes were present in the upper- *vs.* mid-neck. The greatest potential contribution of the current trial is the safety for patients with N1 cervical lymph node involvement. More detailed analyses on the nodal features would be informative—would UNI still be safe for patients with bulky nodes (>3 but <6 cm) or nodes extending to Level III, or nodes showing necrosis and/or extra-nodal extension (16)? Similarly, one may speculate on the feasibility of omitting lower neck irradiation for "low-risk" N2 disease confined entirely to the upper cervical region (i.e., without "mid-neck" involvement) and with a low plasma EBV DNA titre.

- In the same vein, among the 431 patients with a pre-treatment plasma EBV DNA test, 75% (322/431) had a level of <2,000 copies/mL. More detailed analyses on risk-stratification would be needed—for example, would UNI be safe for patients with highly elevated plasma EBV DNA titre, especially for patients staged by MRI without FDG-PET?
- *Discordance between MRI and FDG-PET for nodal staging:* in this study, all patients underwent an MRI of the head and neck to evaluate the extent of the local tumour. However, we are also aware that for the staging of nodal disease, FDG-PET may be more sensitive than MRI, especially for lymph nodes that are equivocal on MRI (17). Given that FDG-PET was only performed in 31% (138/446) of the study subjects, it is plausible that a proportion of N1 patients in this study could have harboured N2 disease instead. Alluding to the scenarios that were aforementioned, this posits another notion if UNI alone is feasible in NPC patients who present with MRI-equivocal, but PET-positive N1-2 disease.
- *Maturity of QOL and TRAEs outcomes:* the investigators are to be commended for including a QOL secondary endpoint that involved the analyses of two recognised and established QOL questionnaires. However, it must be noted that 25% (110/444 for QLQ-C30 and 120/444 for QLQ-H&N35) and 20% (84/444 for QLQ-C30 and 91/444 for QLQ-H&N35) of the study subjects had not completed the baseline and year 3 surveys, respectively. One must thus be cognisant of a potential reporting bias, if the segment of patients who had been unwilling to complete the questionnaires were in fact individuals who had suffered from severe TRAEs. Additionally, while the authors rightly concluded that UNI resulted in fewer TRAEs without compromising disease control in statistical terms, closer scrutiny does indicate that almost all the delayed TRAEs related to lower neck irradiation were mild [1% (2/222) grade 3 dysphagia in WNI]. Thus, if there was indeed a 1.8% difference (upper limit of 95% confidence interval) in 3-year RRFS, one may consider a 1% risk of grade 3 dysphagia with WNI as an acceptable trade-off.
- *Statistical design and maturity of follow-up:* this segues nicely to the next contentious point about this trial with regard to its statistical design. Here, the investigators elected to use a binomial endpoint of 3-year RRFS for their primary analysis of non-inferiority between the WNI and UNI treatment groups. This is not quite comparable to the conventional time-to-event method of defining an acceptable hazard ratio (HR) upper boundary for non-inferiority; then, using Cox regression analyses, one determines if UNI is indeed non-inferior to WNI based on whether the derived 95% confidence upper limit for HR crosses the pre-specified threshold. The choice of 3-year RRFS is particularly relevant in this instance, especially when the event of interest (regional relapse) is known to be delayed, and can occur up to 59 months post-radiotherapy (18). Thus, it is prudent to acknowledge that longer follow-up is needed, not only so that we can assess if the results of non-inferiority still hold with the aggregation of more events, but also for a more accurate assessment of delayed TRAEs. This is concordant with our observation that the 95% confidence interval for the derived HR of RRFS is wide, ranging from 0.25 to 2.09. Arguably, while nodal control is often achieved even among patients with nodal relapse,

the greatest concern remains whether a delay in the eradication of microscopic lymphatic spread will provide a reservoir for subsequent distant metastatic seeding. The 5-year OS rate should be used as a more robust end-point for a trial that aspires to change practice.

Despite the abovementioned limitations, this trial remains pivotal, as it adds to the published literature in support of treatment de-escalation in patients with NPC. Here, the investigators had shown that 3-year RRFS was comparable between WNI and UNI. It remains to be seen if UNI is safe in patients who harbour high-risk features of elevated plasma EBV DNA and/or adverse nodal features like involvement of level III nodal station, bulky size (>3 but <6 cm), nodal necrosis, or extra-nodal extension. On this note, it has been shown that patients who manifest an extreme response to IC have a better disease-free survival compared with those who have a delayed response (19). It will be interesting to test if UNI is feasible for these extreme responders to IC. Besides reducing radiotherapy target volumes, radiotherapy dose reduction is another treatment de-escalation strategy currently being explored in the era of immuno-oncology (IO). There has been much enthusiasm to combine IO with CCRT in head and neck squamous cell carcinoma (HNSCC), but randomised trials thus far have been negative (20,21). A reason for the negative outcomes has been attributed to the high dose prophylactic irradiation of the neck, which would have eradicated the circulating T effector cells that traffic via the lymphatic drainage system (22). Thus, it is hoped that any potential synergy between IO and CCRT may be reinvigorated by lowering the prophylactic neck radiotherapy dose. To this point, a single-institution experience of delivering 30 Gy to the subclinical target volumes in the primary tumour and neck does suggest that such aggressive dose de-escalation is feasible in another viral-associated HNSCC—human papilloma virus-associated oropharyngeal SCC (23). A retrospective single-institution study also reported the clinical outcomes of 347 NPC patients following selective nodal irradiation with a lower elective radiotherapy dose of 36 Gy to the low-risk CTV. The high-risk CTV was defined as lymphatic levels immediately adjacent to the involved nodes with a 1.0 to 1.5 cm margin, while low-risk CTV was defined as 2.0 to 2.5 cm distal lymphatics from the high-risk CTV. Only 1.1% of regional failure occurred exclusively in the low-risk region (24). A randomised phase III trial is currently ongoing to investigate the safety of lowering the dose to the primary tumour and neck based on the tumour response to IC (REACT-lrNPC, NCT04448522, ClinicalTrials.gov).

In summary, the early results of this randomised phase III trial by Tang and colleagues add to the prior 2 prospective studies, supporting the use of UNI in patients with low-risk TNM stage II-IV N0-1 NPC. UNI led to a reduction of delayed hypothyroidism, dysphagia, and skin damage, and QOL was improved compared with WNI. It is however prudent to await longer follow-up to see if these early results of non-inferiority still hold true. Nevertheless, the greatest impact of this study is perhaps its role in catalysing the change in mindset of the community when it comes to conducting future trials of radiotherapy de-escalation for this radiosensitive disease, especially in the era of IO.

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Footnote

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