



# Commentary on “*Elective upper-neck versus whole-neck irradiation of the uninvolved neck in patients with nasopharyngeal carcinoma: an open-label, non-inferiority, multicentre, randomised phase 3 trial*”

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In a 1950 survey amongst head and neck surgeons by Hayes Martin (1), the majority suggested that a threshold of a 10% risk of recurrence should trigger a prophylactic neck dissection. This served to set the stage for our current practice of prophylactic management of the neck.

Berger and colleagues (2) from the MD Anderson Hospital showed that prophylactic neck irradiation [radiotherapy (RT)] for head and neck cancer patients resulted in only 7 of 277 (2.5%) patients having neck recurrence in the electively irradiated region, as compared with 22 of 185 (12%) patients who did not have prophylactic irradiation to the whole neck. Only 1 out of 103 (1%) nasopharyngeal cancer (NPC) patients initially staged as N0 and who had the whole neck irradiated, recurred.

Over in Hong Kong (3), in a study of 196 patients with Stage 1 NPC who were treated with RT, but had neck irradiation omitted, 30% had nodal recurrence in the neck. None of the 7 patients who were treated prophylactically to the neck recurred.

NPC is considered a “midline” tumor. Initial studies by Sham and colleagues (4) showed that the majority of NPC patients had very extensive (and submucosal) involvement of the entire post nasal space, regardless of clinical appearance. It was on this basis that bilateral neck RT was recommended for all NPC patients.

These historical accounts were based on staging by

physical examination as cross-sectional imaging was not readily available in that era, and gives us an idea of how our current concepts for NPC treatment had evolved. The disease burden in patients diagnosed in that era also tended to be more extensive.

Current studies in the era of advanced imaging techniques however, show that magnetic resonance imaging (MRI) had a sensitivity of 100%, specificity of 95%, negative predictive value (NPV) of 100%, positive predictive value (PPV) of 43%, and accuracy of 95% for the primary tumor (5), and thus, a number of tumors might be entirely unilateral. A study of 1,680 MRI staged NPC patients from the Sun Yat-sen University Cancer Center (6), revealed only 112 patients (7%) with lateralized NPC. Within this group, 38% were node negative (N0), 54% had ipsilateral nodal involvement, and 8% had contralateral lymph node metastases; out of which 2 had contralateral nodal metastases only. We now approach a situation where an image-staged N0 neck may be considered a true N0. A study from Hong Kong (7) showed that with computed tomography (CT), about 30% of clinically N0 necks were upstaged to N+. A study comparing MRI with CT (8) showed that MRI upstaged N0 based on CT to N+ in 6% of patients. With the advent of positron emission tomography (PET), a study from the Sun Yat-sen group (9) showed that the sensitivity, specificity and accuracy of PET/CT in diagnosing nodal

metastasis was 93.2%, 98.2% and 95.4%, while that of MRI was 88.8%, 91.2% and 89.9%, respectively ( $P < 0.05$ ).

Another characteristic of neck disease in NPC is its apparent orderly progression, as demonstrated by Sham *et al.* (10). In a study of 271 patients, the authors found that the prevalence of nodal involvement and mean nodal volume decreases as we move caudally down the neck. Furthermore, skipping of neck nodal levels was rare, with only 4% of cases having involvement of the lower neck without associated disease in the ipsilateral upper neck (10). These findings were confirmed by a meta-analysis of 2,920 NPC patients by Ho *et al.* (11) from Singapore. They also found that nodal involvement followed an orderly progression and skip metastases occurred in less than 8% of patients. This disease behavior led the authors to conclude that prophylactic RT of the neck should be extended to at least one nodal level beyond the clinical extent of disease. We can thus infer that for patients with no clinically suspicious nodes, this may mean prophylactic irradiation of only the upper neck.

With this background, many groups have attempted to reduce or omit RT to uninvolved sites. A meta-analysis by Huang and colleagues (12) showed the feasibility of ipsilateral lower neck sparing RT for unilateral or bilateral neck node-negative NPC patients.

In more recent times, there is now greater understanding that the neck nodes are probably an important source for the production of an immune response to the primary tumor. Stanley Order (13) in 1977 postulated that the lymphocytotoxic effect of therapeutic RT might lead to immune depression. We now understand that the tumor draining lymph nodes may be the site for effective T cell generation and can contribute to effective immune checkpoint blockade (14). RT to the primary tumor enhances the release of tumor antigens and activates the interferon type-I pathway. This causes activation of intratumoral dendritic cells (DCs) which then migrate to the lymph nodes, where they in turn activate CD4<sup>+</sup> and CD8<sup>+</sup> T-cells. These cytotoxic T-cells then return to the primary tumor, contributing to the tumouricidal immune response. Irradiating the draining lymph nodes in the neck will eradicate clinical and subclinical metastatic disease, but on the other hand, it will also deplete the cytotoxic immune cell population residing there and thus attenuate the beneficial immune response which might have contributed to tumor eradication. Since the tumor draining lymph nodes are essential for T-cell activation, the practice of ubiquitous prophylactic nodal RT might have to be re-evaluated. The recent reporting of the “30 ROC trial” (15) on oropharyngeal

cancers suggests the feasibility of reducing doses to elective neck nodal areas and points to the direction forward.

It is against this backdrop that we should view this phase 3 trial led by the Sun Yat-sen group (16). Four hundred and forty-six NPC patients with N0–N1 stage disease from 3 centers in China were randomized to upper neck RT alone or whole neck RT. Patients were all staged using contrast enhanced MRI. After a median follow up of 53 months, the 3-year regional relapse free survival was similar in both arms. The acute toxicities were similar in both groups, while the late toxicities favored the upper neck RT alone group. Upper neck RT alone resulted in less hypothyroidism, dysphagia, skin toxicities and soft tissue damage. The authors conclude that “*elective upper neck irradiation of the uninvolved neck provides similar regional control and results in less radiation toxicity compared with standard whole neck irradiation in patients with N0–N1 NPC*”.

In a test simulation carried out by Liu *et al.*, it was noted that it was likely that patients in the group receiving RT to upper neck alone still received a mean dose of approximately 20 Gy to the spared lower neck (17), which was later confirmed by the phase 3 trial authors to be a mean dose of 22 Gy in the trial (18). A point of consideration would be if these results could be translated to proton therapy treatment, especially intensity modulated proton therapy (IMPT), with its superior dose sparing capabilities. To this end, De Felice *et al.* ran a comparison of proton versus photon doses in a patient with N1 disease, showing that proton doses ranged from 10.2 to 13.4 Gy in the spared lower neck; compared to the IMRT photon doses of 28.1 to 36.9 Gy (19). However, in view of the reliability of current day advanced imaging techniques; the orderly progression of neck nodal disease in NPC with extremely rare skip metastasis and the excellent disease control rates, upper neck RT alone remains a practicable option in N0–N1 stage NPC patients.

Overall, this phase 3 study by the Sun Yat-sen group was well-designed and executed and provides definitive level 1 evidence for omitting lower neck RT in eligible patients (16). Besides reducing toxicities, we are also preserving the ability of the body to mount an immune response to the tumor, as well as potentially assisting immunologic agents to work better against the cancer. This thus represents a definite step forward in the management of NPC.

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