



# Association of chemotherapy and radiotherapy for T3N0 nasopharyngeal carcinoma in the area of intensity-modulated radiation therapy

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Nasopharyngeal carcinoma (NPC) is a highly radiosensitive tumor (especially non-keratinizing carcinoma) and radiotherapy (RT) is the mainstay of treatment for newly diagnosed tumors. For early stage NPC, RT alone is the standard treatment while for locally advanced (LA) NPC concurrent chemoradiotherapy (CRT) with or without sequential chemotherapy [induction chemotherapy (IC) or adjuvant chemotherapy] is the standard treatment modality according to current guidelines, while the benefit of adjuvant or induction chemotherapy alone in addition to RT is limited (1,2). Indeed, the benefit of a combined modality approach has been demonstrated by several randomized trials and individual patient data meta-analysis (3). Moreover, in the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC) that included data on 4,806 patients in nineteen trials, with a median follow-up of 7.7 years, the addition of chemotherapy to RT significantly improved overall survival with an absolute benefit at 5 years of 6.3% (95% CI, 3.5–9.1%). The interaction between treatment effect (benefit of chemotherapy) on overall survival and the timing of chemotherapy was significant in favor of concomitant plus adjuvant chemotherapy (HR =0.65; 95% CI, 0.56–0.76) and concomitant without adjuvant chemotherapy (HR =0.80; 95% CI, 0.70–0.93) (3). The same collaborative group published an individual patient data network meta-analysis that included 20 trials and

5,144 patients with LA NPC to determine the optimal timing of chemotherapy. The combination of adjuvant chemotherapy plus concurrent CRT had the highest probability of benefit on overall survival (HR =0.65; 95% CI, 0.56–0.75) when compared with RT alone, while the addition of induction chemotherapy to CRT achieved the highest effect on distant control (HR =0.44; 95% CI, 0.27–0.71) (4).

However, most of the patients included in these meta-analysis were treated with conventional two-dimensional radiotherapy (2DRT) or sometimes three-dimensional conformal radiotherapy (3DCRT). In the last past years, intensity-modulated radiotherapy (IMRT) has gradually replaced 2DRT/3DCRT as it improves target coverage allowing dose escalation and decreasing toxicity. A recently published series of 2,245 patients treated with IMRT found a 5-year overall survival (OS) of 87.4%, and for T3 tumor, a 5-year local control rate of 96.3%, and for N0 patients, a regional control of 98.4% (5).

Currently, distant metastasis remains the major failure pattern for NPC and it is admitted that advanced N-category predicts increased risk of distant metastasis and worse survival. Thereby, for T3N0 NPC, considering the excellent locoregional control with IMRT, the role of chemotherapy, which could lead to a significant morbidity, especially the timing of the use of chemotherapy in combination with RT, is still unclear.

## Concurrent CRT

Concurrent CRT with or without sequential chemotherapy is the standard treatment modality for patients with T3N0M0 NPC (1,2).

In one retrospective study including 440 patients with intermediate risk NPC (stage II and T3N0) treated with IMRT, additional concurrent chemotherapy did not provide any significant survival benefit but increase significantly severe acute toxicities. However, in this series, 94 patients had a T3N0 stage, 70 in the CRT group and only 24 in the RT group (6). It is difficult to obtain a conclusive affirmation because of the low number of T3N0 treated by RT alone.

Some series suggested that in the IMRT area, patients with T3N0 tumors and stage II tumors (T1–2N1 or T2N0 according to 7<sup>th</sup> edition of the UICC/AJCC TNM Staging System) have the same prognosis and should be considered as intermediate risk nasopharynx cancer (6-9).

In one randomized trial evaluating concurrent chemotherapy for patients with stage II NPC (Chinese 1992 staging system), adding chemotherapy didn't statistically improve locoregional relapse-free survival (93.0% *vs.* 91.1%;  $P=0.29$ ) but significantly improved the 5-year OS rate (94.5% *vs.* 85.8%;  $P=0.007$ ), PFS (87.9% *vs.* 77.8%;  $P=0.017$ ), and distant metastasis-free survival (94.8% *vs.* 83.9%;  $P=0.007$ ). Of note, 87% of the patients included had N1–2 stage (restaging according to UICC/AJCC TNM staging system), among whom 10–15% had N2 disease (10).

However, the new TNM staging still discriminate T2/T3 stage based on data of 1,609 patients treated with IMRT. In this series, although the differences in distant-failure free survival and local-failure free survival between T3 and T2 remained insignificant, the difference in OS was statistical significant ( $P=0.043$ ) (11,12).

An ongoing randomized phase III trial will determine the value of concurrent chemotherapy with cisplatin (100 mg/m<sup>2</sup> on day 1, 22, 43) for intermediate risk NPC (T1–2N1/T2–3N0) patients treated with IMRT (NCT02633202).

## Adjuvant chemotherapy

The Intergroup-0099 trial (INT-0099) was the first phase III randomized trial to find an improvement in overall survival rate by adding concurrent chemotherapy and adjuvant chemotherapy to RT alone for patients with LA-NPC (13). Several other randomized studies confirmed

the role of concurrent chemotherapy, and in most of them CRT was associated with adjuvant chemotherapy. Currently, for LA-NPC, CRT with adjuvant chemotherapy is widely adopted in many centers in USA and China. However, compliance with adjuvant chemotherapy is often compromised after CRT, and doesn't exceed 55–75%, even if long-term toxicity doesn't seem increased (14).

Moreover, to evaluate the contribution of adjuvant chemotherapy in addition to concurrent chemotherapy, one trial randomized patients between adjuvant chemotherapy (cisplatin plus fluorouracil) or observation following concurrent CRT with weekly cisplatin. After a median follow-up of 68 months, there was no improvement in 5-year failure-free survival with adjuvant chemotherapy compared with concurrent CRT alone (5-year survival: 75% *vs.* 71%; HR =0.88; 95% CI, 0.64–1.22). Moreover, this trial included patients with a relatively higher risk of distant metastasis (stage III–IVb except T3–T4N0), but even in this subgroup there were no benefit of addition of adjuvant chemotherapy to CRT (14). Another randomized trial tried to evaluate the therapeutic benefit by adding chemotherapy (+C) and/or accelerated-fractionation (AF) for patients with T3–4N0–1M0 NPC. In this trial, concurrent-adjuvant chemotherapy combined with AF significantly reduced failure and cancer-specific deaths. However, both CRT arms had significant increase in acute toxicities ( $P<0.005$ ), and there was a non-significant increase in major late toxicity (36% *vs.* 20%;  $P=0.25$ ) and incidental deaths (9% *vs.* 2%;  $P=0.62$ ) by AF+C treatment. These results must be interpreted with caution: this trial was closed prematurely because of a slow accrual (189 patients included, 464 planned), and compared to INT-0099, the radiation techniques in NPC-9,902 ranged from 2DRT to 3DCRT or IMRT throughout (15). The Hong Kong experiences by Lee et al on 1,593 patients treated using the different techniques suggested that IMRT and 3DCRT improved local control over 2DRT for T3–4 tumors, but similarly for distant relapses, which then begs the question if chemotherapy is still required in the IMRT era (16).

In the last past years, other prognostic factors have been identified and seem to be correlated with the risk of locoregional or distant failure. The most studied is post-treatment EBV DNA that predicts distant failure and poor survival and may be used to select high risk NPC patients for adjuvant chemotherapy. However, in a phase III trial including 789 patients (stage IIB–IVB) randomized in case of detectable EBV DNA after RT or CRT between adjuvant

chemotherapy or observation, adjuvant CT with cisplatin-gemcitabine did not improve survival (17). Another trial of the NRG Oncology group is ongoing (NCT02135042) to confirm these results.

### Induction (or neoadjuvant) chemotherapy

Lan *et al.* retrospectively analyzed 687 patients with stage T3N0–1 NPC (66 T3N0) treated with IMRT and concurrent chemotherapy with or without induction chemotherapy. No significant survival differences were observed between induction chemotherapy plus CRT and RCT cohorts with similar 4-year OS (91.7% *vs.* 92.6%,  $P=0.794$ ), LRFS (92.7% *vs.* 96.8%,  $P=0.138$ ), DMFS (93.5% *vs.* 94.3%,  $P=0.582$ ), and PFS (87.5% *vs.* 91.1%,  $P=0.223$ ). Induction chemotherapy plus CRT group experienced higher rates of grade 3–4 leucopenia and neutropenia (18). Retrospective series that evaluated induction chemotherapy followed by CRT in non-endemic NPC didn't find a survival benefit (19).

Three randomized trials evaluated induction chemotherapy before CRT for LA NPC. However, two of these trials excluded patients with T3N0 tumors (20,21). In the phase III randomized GORTEC 2006 NPC, patients with T2b, T3, T4 and/or N1–N3 tumors were randomized to receive either induction TPF followed by concomitant cisplatin-RT (TPF arm) or concomitant cisplatin-RT alone (reference arm). With a median follow-up of 43.1 months, the 3 years PFS rate (primary end-point) was 73.9% in the TPF arm *vs.* 57.2% in the reference arm (HR =0.44; 95% CI, 0.20–0.97,  $P=0.042$ ). Similarly the 3 years overall survival rate was 86.3% in the TPF arm *vs.* 68.9% in the reference arm (HR =0.40; 95% CI, 0.15–1.04,  $P=0.059$ ). However, the study was prematurely discontinued after inclusion of 83 patients (260 planned) because of poor accrual rate and only 12 patients with T3 tumors were included (22). The results of another randomized trial evaluating induction chemotherapy are awaited (NCT02460887).

Induction chemotherapy can compromise the delivery of concomitant chemotherapy with radiation therapy, so it is mostly indicated in case of bulky lymph nodes metastasis or T4 NPC. For T3N0 NPC stage, the role of induction chemotherapy seems limited.

### Perspectives

In recent years, several agents of molecular targeted therapy

have been developed as alternatives to chemotherapy in association with radiation therapy. The epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) are frequently overexpressed in NPC. To improve the effect of RT, cetuximab, monoclonal antibody against EGFR, have been tested in two phase II trials in combination with CRT with discordant results (23,24). For T3N0M0 tumors, since the benefit of chemotherapy is unclear, development of new agents could lead alternatives to chemotherapy with less toxicity. Nimotuzumab, a novel humanized anti-EGFR monoclonal antibody, is currently recommended by Chinese guidelines with concurrent RT.

Immunotherapy represents another area of research in NPC. Multiple strategies, including EBV-directed adoptive and active immunotherapies, antibodies, EBV lytic cycle induction, and immune-checkpoint blockade have been studied in early phase I/II trial in stage IVc NPC. None have been tested with concurrent RT (25).

### Conclusions

In conclusion, there is limited data evaluating chemotherapy for T3N0 NPC. The risk of distant failure remains low, so induction chemotherapy or adjuvant chemotherapy can probably be omitted. Concurrent CRT is still the standard treatment modality and more data are necessary before considering less aggressive treatment. TNM staging alone cannot identify high risk patients and more biomarkers are necessary to accurately predict outcomes of NPC.

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