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Original Article

# Induction versus Adjuvant Chemotherapy Combined with Concurrent Chemoradiation: What Is Beneficial in Locally Advanced Nasopharyngeal Carcinoma—A 5-Year Comparative Study at a Tertiary Care Center in North India

Kaneez Fatima[1] Asifa Andleeb[1] Shahida Nasreen[1] Mushtaq Ahmad Sofi[1] Ulfat Ara Wani[1] Malik Tariq Rasool[1] Arshad Manzoor Najmi[1] Shaqul Qamar[1] Nazir Ahmad[1] Rubiya Ryhan[1]

[1] Department of Radiation Oncology, Medical Oncology, Sheri Kashmir Institute of Medical Sciences (SKIMS), Soura UT, Jammu and Kashmir, India

Address for correspondence Kaneez Fatima, MD, Department of Radiation Oncology, Sheri Kashmir Institute of Medical Sciences (SKIMS), Soura UT 190012, Jammu and Kashmir, India (e-mail: kanz10kgl24@gmail.com).

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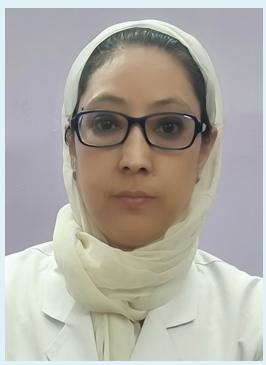
## Abstract



Kaneez Fatima

**Background** In locally advanced nasopharyngeal cancer (LANPC), concurrent chemoradiotherapy (CCRT) has been established as the current standard of care, but recently, the addition of induction chemotherapy to CCRT has presented an attractive multidisciplinary approach.

**Objectives** The aim of the study was to explore the clinical outcome of induction chemotherapy (IC) followed by CCRT and CCRT followed by adjuvant chemotherapy (AC) in LANPC.

**Material and Methods** In this propensity score–matched retrospective cohort study, we enrolled LANPC patients from October 2016 to June 2022. Study variables were evenly distributed by propensity score matching. Independent prognostic factors were identified using Cox regression analysis, and the outcome between the two chemotherapy treatment combinations was compared for patients in different subgroups.

**Result** A total of 80 patients were included in the study. Survival outcomes indicated that the IC followed by CCRT group (IC + CCRT) achieved a higher 5-year overall survival (OS; 90 vs. 81%, $p = 0.253$), failure-free survival (FFS; 80 vs. 77.50%, $p = 0.17$), and distant metastasis-free survival (DMFS; 88 vs. 82.50%, $p = 0.314$) compared with the CCRT followed by AC group (CCRT + AC), although it was not statistically significant. The stratified analysis revealed that IC followed by CCRT (IC + CCRT) was associated with significantly improved OS (hazard ratio [HR] = 0.212; 95% confidence interval [CI] = 0.014–3.16; $p = 0.0026$) in N2 disease. However, the superiority of CCRT followed by AC (CCRT + AC) was only observed in LRRFS (HR = 0.45; 95% CI = 0.05–0.89; $p = 0.036$) for the T4 subgroup.

**Conclusion** In patients with LANPC, especially with T3 or N2 disease, IC should be strongly considered followed by CCRT.

**Keywords**

- chemoradiation
- induction chemotherapy
- locally advanced nasopharyngeal carcinoma
- adjuvant chemotherapy

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## Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy arising from the mucosa of the nasopharynx, most of which occurs in the upper and lateral walls, particularly in the pharyngeal recess.[1] As per GLOBOCAN 2020, 133,354 cases of NPC and 80,008 deaths have been estimated globally, with the highest incidence in regions like Southeastern Asia, Southern China, and Northern Africa.[2] More than 70% of NPC patients have advanced disease at presentation due to late diagnosis.[3] Because of the unique radiosensitive behavior of NPC cells, radiation therapy (RT) is regarded as the mainstay of treatment. RT alone is considered as the treatment of choice in early-stage nasopharyngeal carcinoma (ESNPC).[4] However, the addition of chemotherapy to RT improved the survival in locally advanced nasopharyngeal cancer (LANPC), compared with RT alone.[5] Adjuvant chemotherapy (AC) after concurrent chemoradiation (CCRT) further benefits these patients in terms of the overall survival (OS).[6] However, most of the patients are not able to tolerate AC because of the severe toxicity of CCRT, which limits the widespread use of AC. Also, some of the studies have shown the undefined role of adding AC to CCRT.[7] Chen et al failed to show any significant survival benefit with CCRT followed by AC (CCRT + AC) in LANPC as compared with CCRT alone. This study also confirmed severe toxicity with low compliance of the patients.[8] Therefore, a policy should be developed to improve efficacy with better compliance with the treatment and systemic control. Induction chemotherapy (IC) is an option in LANPC and has attracted a lot of attention as it has better patient compliance and can eradicate micrometastasis.[9] A phase 3 randomized controlled trial has proved that the addition of IC followed by CCRT (IC + CCRT) has a 5-year survival advantage as compared with CCRT alone.[10] IC, followed by CCRT also improves progression-free survival, locoregional, and distant control rates.[11] However, the survival advantage in both IC + CCRT and CCRT + AC has been proved by indirect comparison as CCRT, the comparator. In this retrospective study, we compare the efficacy of IC + CCRT with CCRT + AC in LANPC.

## Materials and Methods

### General Patient Details and Participants

We retrospectively analyzed the patient data from October 2016 to June 2022 at our cancer institute. The patients were of Kashmiri ethnicity. Patient data were collected from case files and radiotherapy files. Informed consent was obtained from all the patients. Ethical clearance was obtained from the ethical board of the institution. We included newly diagnosed NPC patients with (1) histopathologically confirmed NPC, (2) stage II to IVA as per 7th and 8th editions of the AJCC staging system, (3) those who received IC with CCRT, and (4) those who received AC with CCRT based on intensity-modulated radiotherapy (IMRT). We excluded patients with (1) stage I and IVB, (2) patients who received only CCRT or RT alone, and (3) patients who dropped out or did not complete the induction or AC (►Fig. 1).

### Aims and Objectives

The primary aim of this study is to explore the role of IC + CCRT and CCRT + AC in LANPC. OS was the primary end point of our study. Secondary end points were failure-free survival (FFS), locoregional relapse-free survival (LRRFS), and distant metastasis-free survival (DMFS).

### Study Methodology

Routine pretreatment evaluation includes (1) complete history and physical examination, (2) routine blood tests and biochemistry profile, (3) mirror and fiberoptic examination with biopsy, (4) magnetic resonance imaging (MRI) of the nasopharynx and neck, (4) computed tomography (CT) of the chest with or without contrast, and (5) whole-body bone scan and 18-fluorodeoxyglucose positron emission tomography/CT, if indicated. Pretreatment audiogram was also performed in all patients.

### Radiotherapy

All patients received radiation treatment with IMRT. All the patients received one fraction per day for 5 days a week. Target volumes were delineated using International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62. The prescribed radiation dose was defined as follows: planning target volume (PTV) of the primary tumor gross tumor volume (GTV nx; including the primary tumor and enlarged lymph nodes) received 70 to 72 Gy; PTV of the nodal gross tumor volume (GTVnd), 66 to 70 Gy; PTV of CTV1 (i.e., high-risk regions) received 60 to 63 Gy; and PTV of CTV2 (i.e., low-risk regions) received 50 to 54 Gy in 28 to 33 fractions. The CTV1 was defined to encompass the entire nasopharyngeal mucosa, the GTVnx, and a 5-mm submucosal margin. CTV2 was drawn to encompass CTV1 with a margin of 5 to 10 mm, and 2 to 3 mm posteriorly if it was close to the brainstem or spinal cord, as well as any lymphatic regions that might have been implicated. An additional 5-mm margin was added to make the PTV. The various organs at risk (OARS) and dose constraints are shown in the table (►Table 1).

### Chemotherapy

The regimens for IC and AC were based on platinum agents. In IC, the patient received the following regimens: cisplatin plus 5-fluorouracil (PF; injection cisplatin 100/$m^2$ on day 1 and injection 5-fluorouracil 1,000 mg/$m^2$ continuous infusion for 4 days)[12]; docetaxel plus cisplatin (TP; injection docetaxel 75 mg/$m^2$ and injection cisplatin 75 mg/$m^2$ on day 1)[13]; and docetaxel plus cisplatin plus 5-fluorouracil (TPF; injection docetaxel 70 mg/$m^2$ on day 1, injection cisplatin 75 mg/$m^2$ on day 1, and injection 5-fluorouracil 1,000 mg/$m^2$ continuous infusion for 4 days).[14] Patients received two to three cycles of IC and each cycle was repeated after 21 days. In the adjuvant setting, patients mainly received cisplatin plus 5-fluorouracil-based chemotherapy (PF; injection cisplatin 100 mg/$m^2$ on day 1 and injection 5-fluorouracil 1,000 mg/$m^2$) continuous infusion for 4 days and (P; injection cisplatin 100 mg/$m^2$ every 3 weeks for 3–4 cycles). In CCRT, patients received either injection cisplatin 40 mg/$m^2$ weekly or 100 mg/$m^2$ 3 weekly with RT.

 

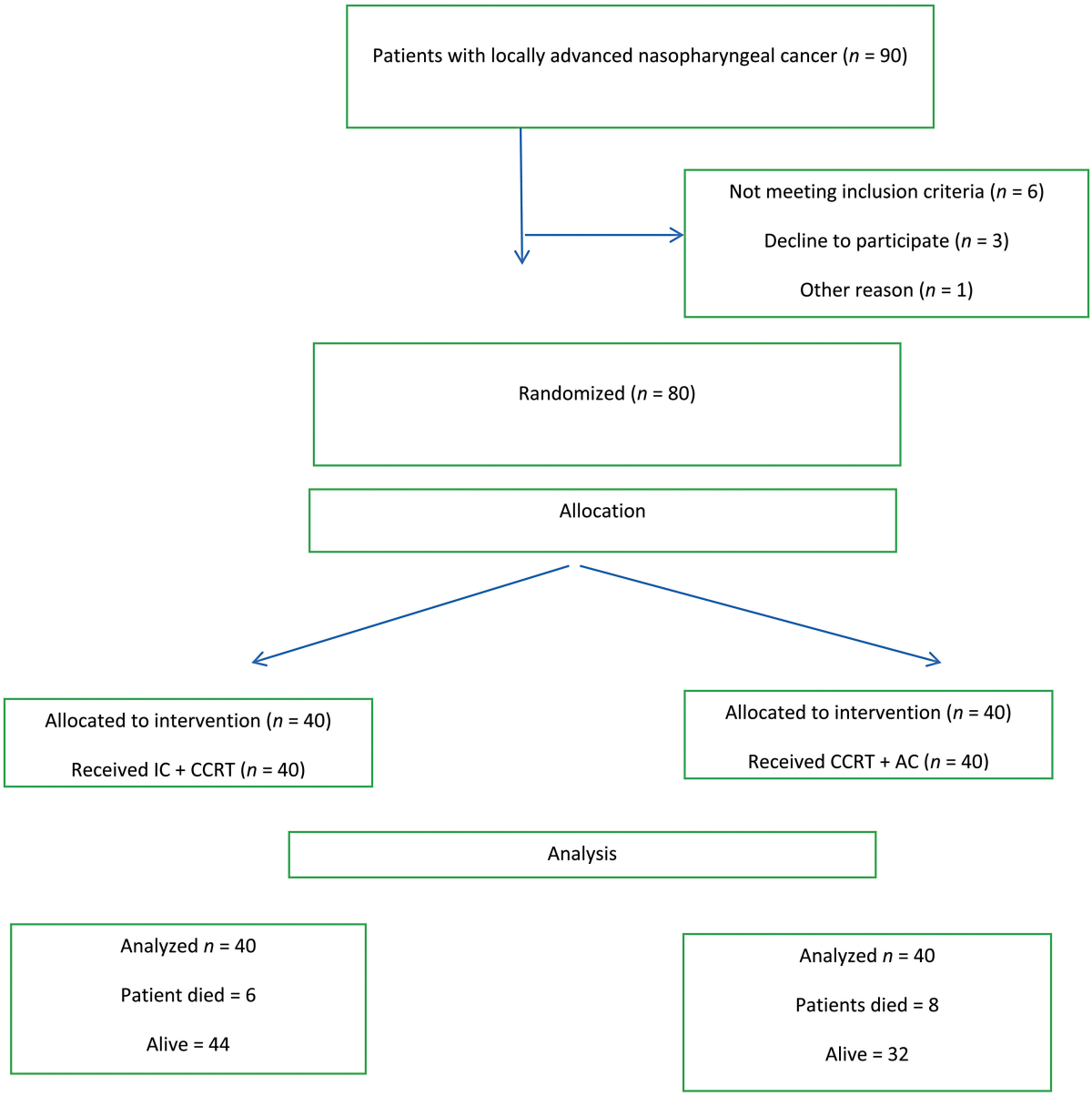


**Fig. 1** Console diagram. Enrollment.

**Table 1** Doses: D95 = 95% of the volume

| **Dmax = maximum dose to 0.03 mL of the volume** | |
|---|---|
| Structure | Dose constraints |
| Bone mandible | MAX <70 Gy |
| TMJ | D0.03 mL (Gy) <70 up to 75 Gy allowed |
| Brainstem PRV03 | D0.03 mL (Gy) 54–58 Gy |
| Spinal cord | MAX 45 Gy; MAX PRV (CORD + 5 mm) 48 Gy |
| Parotid | Mean dose <26 Gy |
| Sabmandibular glands | Mean dose of <39 Gy OR 40 Gy |
| Cochlea | MEAN <35 Gy; MAX <55 Gy |
| Chiasm | <55 Gy D0.03 CC GY |
| Optic nerve | MAX 55 Gy D0.03 mL Gy |
| Eyes | < MAX 55Gy D0.03 mL Gy |

Abbreviations: PRV, planning organ at risk volume; TMJ, temporomandibular joint.

 

### Follow-Up End Points

The time between the initial pathology diagnosis and the final visit or death was considered as the follow-up duration. In IC, group response assessment was done using the response evaluation criteria in solid tumors (RESCIST) criteria. Patients were followed up every 3 months in the first year, every 6 months in the second year, every 8 months in the third to fifth years, and annually thereafter with history, physical examination, complete head and neck examination, and radiological imaging. If clinical symptoms or imaging revealed a recurrence or residual focus, a biopsy was performed. Endpoints included the 5-year OS, FFS, LRRFS, and DMFS. The OS is defined as the time of disease diagnosis to death due to any cause. FFS is defined from the start of treatment to any disease event like recurrence or death due to any cause. The LRRFS is defined from the start of treatment to locoregional recurrence. DMFS has been calculated from the start of treatment to the occurrence of distant failures.

### Statistical Analysis

Without using replacement, propensity score matching (PSM) was calculated using the nearest-neighbor method with a stringent caliper of 0.01. Continuous variables were converted into categorical variables according to interquartile range (IQR; age at diagnosis), clinical experience (hemoglobin [HGB]) in Sun Yat-Sen University Cancer Center (SYSUCC). The chi-squared test was used to contrast the categorical variables between CCRT + AC and IC + CCRT; and OS, FFS, LRLFS, and DMFS survival outcomes were assessed using the Kaplan–Meier technique and compared using the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Other analyses and the creation of figures were done using SPSS version 23.0 (SPSS Inc., Chicago, Illinois, United States). A two-sided p value of less than 0.05 was considered significant unless otherwise specified.

## Results

### Baseline Characteristics

A total of 80 patients were included in the study (40 patients in each group). The median age of presentation was 55 years in each group.

The baseline characteristics were well balanced between the two groups (►Table 2). The median follow-up in both the groups (IC+ CCRT and CCRT +AC) were 50 months (IQR = 35–65) and 55 months (IQR = 45–60), respectively. The survival outcome between the two groups was different. The IC +CCRT group achieved a higher 5-year OS (90 vs. 81% $p = 0.253$), FFS (80 vs. 77.50%, $p = 0.17$), and DMFS (88 vs. 82.50%, $p = 0.314$), except for the 5-year LRRFS (90% vs. 92%; $p = 0.954$) compared with CCRT + AC group (►Fig. 2)

### Toxicity Profile

The toxicity profile was comparable between the two groups; the only exception was that the grade 3/4 hematological toxicity was slightly higher in the CCRT + AC group (►Table 3). None of the patients develop grade 3/4 radiation toxicity in both the groups.

### Univariate Cox Regression Analysis

In the univariable analysis, we included both demographic and clinicopathologic profile. TN category, HGB, and LDH were significant predictive prognostic factors (►Table 4). The adjusted HR for 5-year OS, LRRFS, and DMFS was 0.525 (95% CI = 0.171–1.613, $p = 0.261$) and 0 0.562 (95% CI = .178–1.795, $p = 333$), respectively, with IC + CCRT being superior to CCRT + AC. While as the 5-year LRRFS is higher in the CCRT with AC group (CCRT + AC), the HR was 0.956 (95% CI = 0.203–4.514, $p = 0.955$). Between the two treatment groups, FFS remained similar, with HR = 0.515 (95% CI = 0.193–1.376, $p = 0.186$; ►Table 5).

### Subgroup Analysis

A stratified analysis was conducted according to the TN category and the level of HGB and LDH to further distinguish between the survival differences in these treatment modalities. Among patients with T3 (TNM) NPC, 19 and 18 patients receiving IC with CCRT and CCRT + AC, respectively, were selected for subgroup analysis. The IC + CCRT group outperformed the CCRT + AC group in terms of 5-year OS (94 vs. 89%, $p = 0.012$), FFS (90 vs. 77.8%, $p = 0.039$), and LRRFS (95 vs. 89.9%, $p = 0.035$). However, no significant difference has been observed in DMFS (95 vs. 90%%, $p = 0.307$; ►Fig. 3). Additionally, the 5-year OS in the IC + CCRT group was significantly different in patients with N2 NPC (87.5 vs. 75.0%, $p = 0.026$) as compared the CCRT + AC group (►Table 6; ►Fig. 4). However, CCRT + AC yielded a better LRRFS in patients with T4 NPC (HR = 0.212; 95% CI = 0.014–3.16; $p = 0.0026$).

To investigate the value of further chemotherapy, a stratified analysis of the chemotherapy regimens and cycles was also performed. There were no statistically significant differences in any of the outcomes between the two groups.

## Discussion

In patients with LANPC, CCRT with additional chemotherapy is considered a promising treatment. However, whether the best timing of additional chemotherapy is before or after CCRT remains unclear. Clinical trials revealed that patients with LANPC showed remarkable improvement in tumor control as well as survival with the addition of IC to CCRT.[15–17]

But CCRT + AC is still an option as per the National Comprehensive Cancer Network (NCCN) guidelines (2023), in LANPC, as is also evidenced by some of the published data.[18] IC is considered a more practical and effective intense therapy strategy due to patients' limited tolerance for AC and the uncertainties surrounding its efficacy. Additionally, because it is performed prior to CCRT, patients have better overall health and can handle chemotherapy better.[19,20] However, not much information is available regarding the comparison of the two regimens except for the study conducted by Lee et al, which consisted of six arms.[21] This study is a retrospective study, comparing the effectiveness of IC and AC with CCRT in

 

**Table 2** Baseline characteristics and treatment details of the patients in the matched dataset

| Variables | Category | Group | | | | *p*-value |
|---|---|---|---|---|---|---|
| | | IC + CCRT | | CCRT + AC | | |
| | | *n* | % | *n* | % | |
| Age group | <36 | 8 | 20.00 | 7 | 17.50 | 0.896 |
| | <37–41 | 10 | 25.00 | 9 | 22.50 | |
| | 45–51 | 7 | 17.50 | 6 | 15.00 | |
| | >51 | 15 | 37.50 | 18 | 45.00 | |
| Gender | M | 37 | 92.50 | 35 | 87.50 | 0.448 |
| | F | 3 | 7.50 | 5 | 12.50 | |
| HPE | 1 | 3 | 7.50 | 1 | 2.50 | 0.472 |
| | 2 | 8 | 20.00 | 11 | 27.50 | |
| | 3 | 29 | 72.50 | 28 | 70.00 | |
| T stage | T1 | 5 | 12.50 | 6 | 15.00 | 0.126 |
| | T2 | 6 | 15.00 | 7 | 17.50 | |
| | T3 | 19 | 47.50 | 18 | 45.00 | |
| | T4 | 10 | 25.00 | 9 | 22.50 | |
| N stage | N0 | 5 | 12.50 | 7 | 17.50 | 0.07 |
| | N1 | 21 | 52.50 | 20 | 50.00 | |
| | N2 | 8 | 20.00 | 7 | 17.50 | |
| | N3 | 6 | 15.00 | 5 | 12.50 | |
| ALB | <50 | 32 | 80.00 | 36 | 90.00 | 0.196 |
| | >50 | 8 | 20.00 | 4 | 10.00 | |
| LDH | <150 | 25 | 62.50 | 26 | 65.00 | 0.451 |
| | >150 | 15 | 37.50 | 13 | 32.50 | |
| HGB (M/F) | <12/10 | 5 | 12.50 | 6 | 15.00 | 0.739 |
| | >12/10 | 35 | 87.50 | 34 | 85.00 | |
| Smoking | Y | 28 | 70.00 | 26 | 65.00 | 0.602 |
| | N | 12 | 30.00 | 14 | 35.00 | |
| IC/AC regimen | TPF | 12 | 30.00 | 0 | 0.00 | 0.512 |
| | TP | 10 | 25.00 | 0 | 0.00 | |
| | PF | 16 | 40.00 | 24 | 60.00 | |
| | P | 0 | 0.00 | 13 | 32.50 | |
| | Others | 2 | 5.00 | 3 | 7.50 | |
| Cycles | 1 | 3 | 7.50 | 6 | 15.00 | 0.213 |
| | 2 | 24 | 60.00 | 14 | 35.00 | |
| | >3 | 13 | 32.50 | 20 | 50.00 | |

Abbreviations: AC, adjuvant chemotherapy; ALB, albumin; CCRT, concurrent chemo radiation; HGB, hemoglobin; IC, induction chemotherapy; LDH, serum lactate dehydrogenase; M/F, male/female; P, cisplatin; PF, cisplatin and 5-florouracil; TP, docetaxel and cisplatin; TPF, docetaxel, cisplatin, and 5-florouracil; WHO, World Health Organization.
Note: Values are presented as number (%).
All variables were measured before initial treatment.

LANPC, and thus offers important insights into these treatment plans in clinical practice. Multiple systematic reviews also suggest that IC before CCRT in patients with LANPC may impact tumor control as compared with chemoradiation without additional chemotherapy.[22–24] Several systematic reviews suggested that IC prior to CCRT is associated with superior OS and progression-free survival.[25] The Hong Kong NPC study group, in a phase 3 randomized trial, showed a survival advantage when comparing IC followed by chemoradiation to chemoradiation followed by AC.[26] A recent American Society of Clinical Oncology consensus guidelines recommended IC + CCRT in LANPC.[27] Our study revealed IC + CCRT provides

 

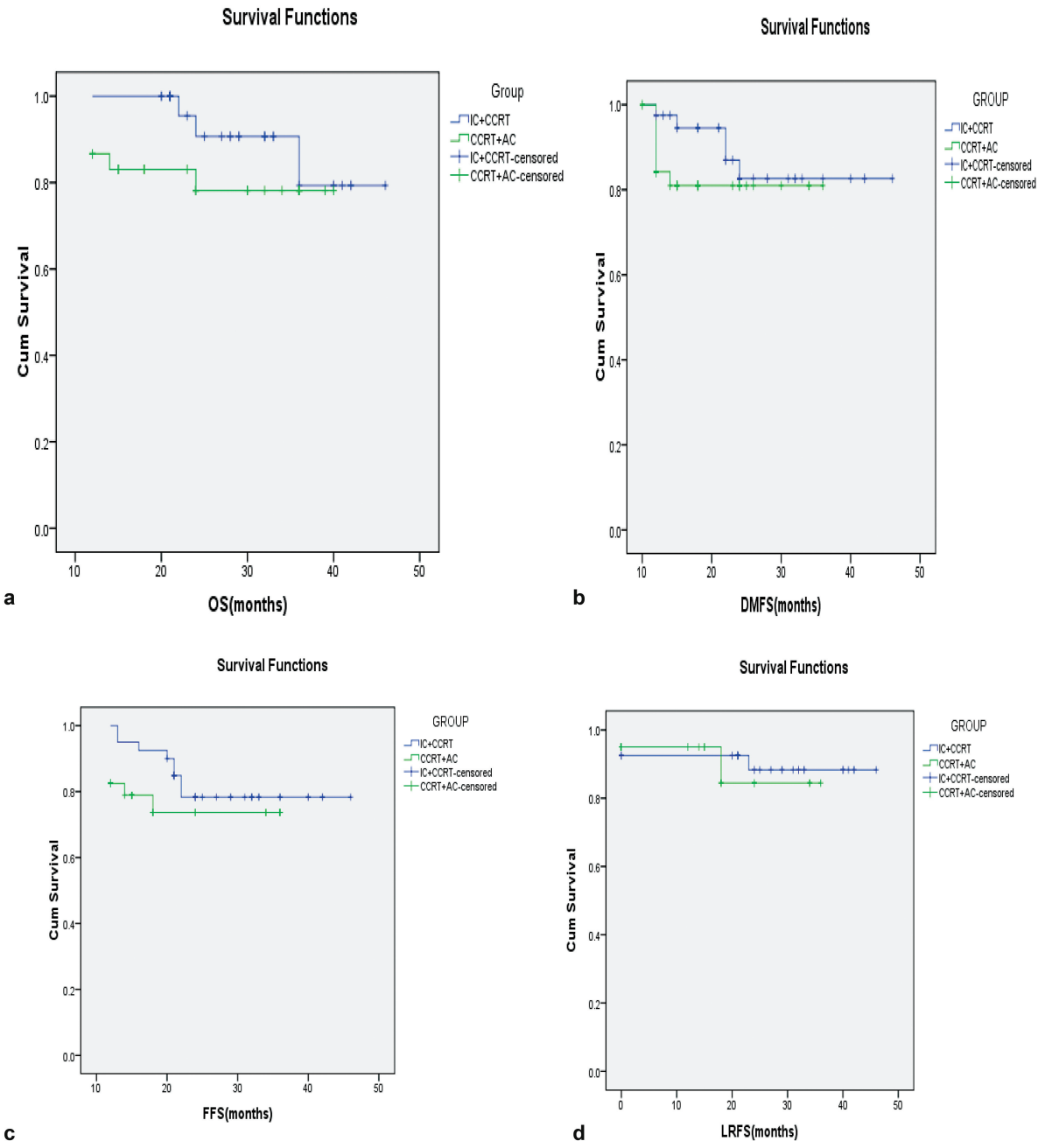


**Fig. 2** Kaplan–Meier survival curves of (**a**) OS, (**b**) DMFS, (**c**) FFS, and (**d**) LRFS for patients stratified as IC + CCRT and CCRT + AC groups in the matched data set. AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; DMFS, distant metastasis-free survival; FFS, failure-free survival; IC, induction chemotherapy; LRFS, locoregional free survival; OS, overall survival.

favorable OS, which is in contrast to a study that found AC yielded better OS as compared with IC.[24] These contrasting results could be due to several possible reasons. First, all the patients in our study received IMRT, in contrast to the given research. Second, a retrospective analysis found that IMRT is more effective at locoregional control in NPC patients than two-dimensional conventional radiotherapy (2DCRT; 92.7 vs. 86.8%; $p = 0.007$).[28] Therefore, any therapeutic benefit offered by AC might be marginal. Subgroup analysis was performed based on the T stage category. According to Cox regression analysis, IC + CCRT improved the OS, FFS, and DMFS in T3 NPC patients, while as AC + CCRT improved the LRRFS in T4 NPC patients. These findings can be explained by the following reasons. First, compliance with AC is poor due to acute toxicities as evidenced by several studies.[29] So, it is possible that AC will not offer the potential survival benefits it may have due to low compliance and a higher incidence of side effects. Second, the superior survival of IC + CCRT compared with CCRT alone and similar outcomes between CCRT alone and CCRT +AC were based on the patients having stage III to IV cancer excluding (T3–T4 NO) NPC,[9] but our study did not exclude patients with the stage T3–T4 NO. This could indicate that there is enhanced potential for favorable effects with AC on remote control. In the stratified analysis, patients with N2

 

**Table 3** Grade 3 to 4 toxicities during IC + CCRT and CCRT + AC in LANPC patients

| Toxicities | IC + CCRT ($n = 40$) | | CCRT + AC ($n = 40$) | | *p*-value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| Neutropenia | 6 | 15 | 13 | 32.5 | <0.001 |
| Leucopenia | 7 | 17.5 | 14 | 35 | <0.001 |
| Thrombocytopenia | 2 | 5 | 3 | 7.5 | >0.05 |
| Anemia | 3 | 7.5 | 4 | 10 | >0.05 |
| Vomiting | 1 | 2.5 | 1 | 2.5 | >0.05 |
| Hepatotoxicity | 0 | 0 | 0 | 0 | |
| Weight loss | 1 | 2.5 | 1 | 2.5 | >0.05 |
| Mucositis | 1 | 2.5 | 1 | 2.5 | >0.05 |
| Xerostomia | 0 | 0 | 0 | 0 | |
| Trismus | 0 | 0 | 0 | 0 | |
| Skin fibrosis | 0 | 0 | 0 | 0 | |

Abbreviations: CCRT + AC, concurrent chemoradiation followed by adjuvant chemotherapy; IC + CCRT, induction chemotherapy followed by concurrent chemotherapy; LANPC, locally advanced nasopharyngeal cancer.

**Table 4** Univariable Cox analysis of the effect of prognostic factors in the matched dataset

| OS | | | | | | FFS | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variables | categories | Sig. | | 95.0% CI for HR | | Sig. | | 95.0% CI for HR | |
| | | | HR | Lower | Upper | | HR | Lower | Upper |
| Age group | <36 | | Ref | | | | Ref | | |
| | <37–41 | 0.721 | 1.386 | 0.231 | 8.322 | 0.083 | 4.45 | 0.822 | 24.101 |
| | 45–51 | 0.512 | 1.931 | 0.27 | 13.808 | 0.672 | 1.499 | 0.23 | 9.757 |
| | >51 | 0.892 | 1.118 | 0.225 | 5.553 | 0.041 | 5.917 | 1.071 | 32.682 |
| Sex | F | 0.386 | Ref | | | 0.823 | Ref | | |
| | M | | 0.040 | 2.77 | 7.941 | | 1.31 | 1.39 | 1.23 |
| HPE | 1–2 | 0.95 | Ref | | | 0.665 | Ref | | |
| | 3 | | 0.963 | 0.296 | 3.129 | | 1.361 | 0.337 | 5.496 |
| T stage | 1 | | Ref | | | | Ref | | |
| | 2 | 0.031* | 3.56 | 0.315 | 4.135 | 0.111 | 0.115 | 0.008 | 1.642 |
| | 3 | 0.205 | 0.231 | 0.024 | 2.228 | 0.094 | 0.148 | 0.016 | 1.39 |
| | 4 | 0.021* | 2.539 | 0.687 | 9.382 | 0.025* | 0.808 | 0.177 | 3.682 |
| N stage | 0 | | Ref | | | | Ref | | |
| | 1 | 0.028 | 0.1 | 0.013 | 0.78 | 0.937 | 1.33 | 7.53 | 2.33 |
| | 2 | 0.416 | 0.472 | 0.077 | 2.89 | 0.941 | 7.08 | 4.03 | 1.24 |
| | 3 | 0.011* | 0.412 | 0.004 | 0.89. | 0.031* | 1.02 | 5.78 | 1.78 |
| ALB (g/dL) | <50 | 0.193 | Ref | | | 0.076 | Ref | | |
| | >50 | | 0.242 | 0.028 | 2.054 | | 13.947 | 0.762 | 255.195 |
| LDH (U/L) | <150 | 0.041* | Ref | | | 0.106 | Ref | | |
| | >150 | | 0.278 | 0.052 | 1.501 | | 6.132 | 0.679 | 55.387 |
| HGB (g/L) | <12/10 | 0.137 | Ref | | | 0.228 | Ref | | |
| | >12/10 | | 0.278 | 0.052 | 1.501 | | 2.901 | 0.514 | 16.372 |
| Smoking | N | 0.763 | Ref | | | 0.842 | Ref | | |
| | Y | | 0.832 | 0.252 | 2.751 | | 0.86 | 0.196 | 3.773 |

Abbreviations: ALB, albumin LDH = serum lactate; CI, confidence interval; FFS, failure-free survival; HGB, hemoglobin; HPE 1, (WHO GRADE 1), 2 (WHO GRADE 2), 3 (WHO GRADE 3); HR, hazard ratio; LDH, serum lactate dehydrogenase; OS, overall survival; WHO, World Health Organization.
*P-value < 0.05 in Cox regression analysis of variables.

 

**Table 5** HR and 95% CI for survival in both groups (IC + CCRT vs. CCRT + AC)

| Survival | HR (95% CI) | *p*-value |
|---|---|---|
| OS | 0.525 (0.171–1.613) | 0.261 |
| DMFS | 0.565 (0.178–1.795) | 0.333 |
| LRRFS | 0.956 (0.203–4.514) | 0.955 |
| FFS | 0.515 (0.193–1.375) | 0.186 |

Abbreviations: CCRT + AC, concurrent chemoradiation followed by adjuvant chemotherapy; CI, confidence interval; DMFS, distant metastasis free survival; FFS, failure-free survival; HR, hazard ratio; IC + CCRT, induction chemotherapy followed by concurrent chemotherapy; LRRFS, locoregional relapse-free survival; OS, overall survival.

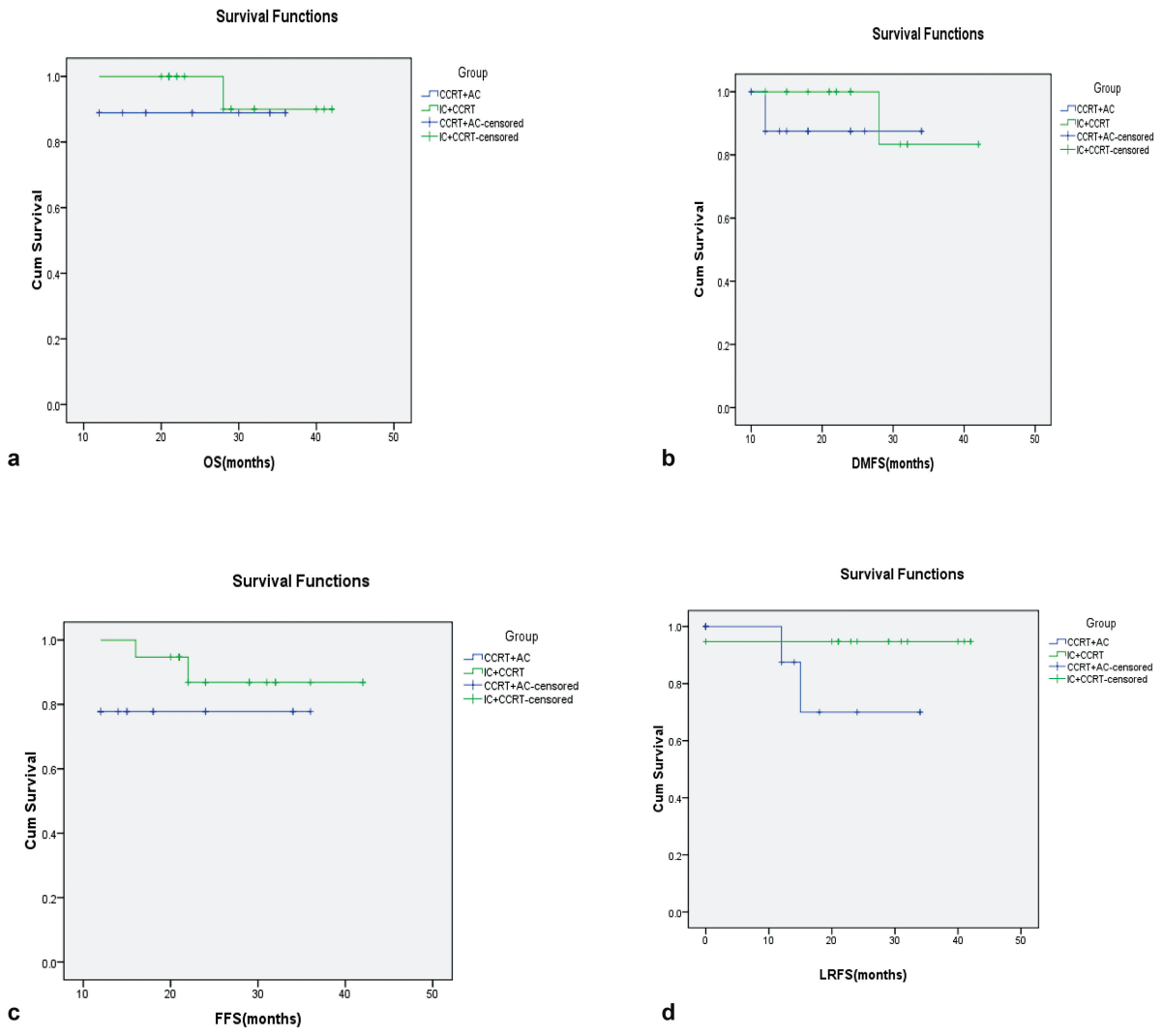


**Fig. 3** Kaplan–Meier survival curves of (**a**) OS, (**b**) DMFS, (**c**) FFS, and (**d**) LRFS and for patients with T3 receiving IC + CCRT or CCRT + AC treatment. AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; DMFS, distant metastasis-free survival; FFS, failure-free survival; IC, induction chemotherapy; LRRFS, locoregional relapse-free survival; OS, overall survival.

nodal stage who were treated with IC + CCRT had a significant 5-year OS. Similarly, several studies also demonstrated prolonged OS in patients with N2–N3 disease treated with IC + CCRT compared with CCRT + AC.[30] The reason could be explained by the downstaging property of IC. Different regimens of IC + CCRT in comparison to CCRT + AC do not show a significant difference. On the other hand, a trial having six study arms revealed that IC with cisplatin and capecitabine followed by CCRT was linked to a better progression-free survival compared with CCRT + AC with cisplatin and 5-FU regimen.[21] The survival advantage of IC may be diminished by the relatively mild intensity of IC agents because in our study, cisplatin and capecitabine regimens were rarely used. Additionally, Zhang et al demonstrated an absolute benefit of 8.8

 

**Table 6** HR and 95% CI for each subgroup analysis in the IC + CCRT group

| Labels | OS | | FFS | |
|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| **T category** | | | | |
| T1 | 2.31 (1.533–3.52) | 0.895 | 1.7 (0.45–6.95) | 0.929 |
| T2 | 0.991 (5.34–1.86) | 1 | 1.99 (0.123–8.65) | 0.983 |
| T3 | 3.55 (3.69–8.34) | 0.041 | 1.07 (0.121–9.65) | 0.031 |
| T4 | 2.33 (1.54–3.51) | 0.963 | 1.76 (0.18–16.72) | 0.633 |
| **N category** | | | | |
| N0 | 0.36 (0.002–3.96) | 0.308 | 0.7 (0.18–3.38) | 0.227 |
| N1 | 0.036 (0.001–1.13) | 0.059 | 0.045 (0.002–1.16) | 0.062 |
| N2 | 0.212 (0.014–3.16) | 0.026 | 0.094 (0.007–1.31) | 0.079 |
| N3 | 4.65 (4.58–4.71) | 0.955 | 0.156 (0.008–2.89) | 0.212 |
| **ALB** | | | | |
| <50 | 1.03 (0.115–9.24) | 0.975 | 0.557 (0.068–4.531) | 0.584 |
| >50 | 18.76 (0.264–23.98) | 0.178 | 3.1 (0.145–66.4) | 0.469 |
| **LDH** | | | | |
| <150 | 2.59 (0.92–4.08) | 0.973 | 1.34 (0.54–2.44) | 0.456 |
| >150 | 1.91 (0.213–17.22) | 0.562 | 4.97 (0.521–47.5) | 0.163 |
| **HGB** | | | | |
| <12/10 | 2.45 (0.23–17.07) | 0.637 | 0.91 (0.09–8.79) | 0.523 |
| >12/10 | 5.33 (3.8–7.74) | 0.979 | 0.025 (2.28–2.68) | 0.122 |
| **Regimen** | | | | |
| TPF | 2.25 (0.71–3.17) | 0.603 | 0.84 (0.67–2.55) | 0.333 |
| TP | 1.98 (5.91–6.65) | 0.929 | 5.21 (2.97–9.14) | 0.894 |
| PF | 1.41 (4.13–4.84) | 0.918 | 1.21 (1.018–2.13) | 0.886 |
| Others | 8.62 (0.04–17.84) | 0.997 | 1.04 (5.76–7.88) | 0.865 |
| **Cycles** | | | | |
| 1 | 3.91 (0.62–24.03) | 0.531 | 2.9 (0.69–7.14) | 0.844 |
| 2 | 3.17 (3.1–3.24) | 0.997 | 1.98 (1.35–2.91) | 0.997 |
| >3 | 0.42 (4.06–4.33) | 0.998 | 0.908 (6.14–13.41) | 1 |

Abbreviations: ALB, albumin; CI, confidence interval; FFS, failure- free survival; HGB, hemoglobin; HR, hazard ratio; IC + CCRT, induction chemotherapy followed by concurrent chemotherapy; LDL, low-density lipoprotein; OS, overall survival; PF, cisplatin and 5-fluorouracil; TP, taxanes and cisplatin; TPC, taxanes, cisplatin, and 5-fluorouracil.

and 4.3% in 3-year LRRFS and OS, respectively, with cisplatin and gemcitabine-based IC followed by chemoradiation over CCRT for stage III to IVA NPC.[15] As more studies reveal the enhanced therapeutic efficacy offered by IC with various regimens, it is important to investigate the greater survival advantage associated with IC + CCRT.

The PSM method, which balances the baseline characteristics of the included patients to limit the possibility of confounders, is the primary benefit of our study. Second, the inclusion of pretreatment HGB, LDH, and ALB in adjusted variables increases the likelihood that a survival benefit would be seen. There are certain limitations of our study. First is the retrospective nature of the study. Second, the distribution of the additional chemotherapy that patients completed between the two groups was quite uneven. It may be suggested that the patients receive timely CCRT treatment if the tumor is not controlled during the early cycles of IC. Additionally, due to the significant toxicity of the cisplatin- and 5-fluorouracil-based regimen, single-agent cisplatin (100 mg/m$^2$) with omitted 5-fluorouracil was frequently selected for intolerable patients. The other regimens include TPF (12%) and TP (10%; ►Table 2). Due to the retrospective nature of the study, we acknowledge that the above-mentioned factors are flaws and therefore we recommend further prospective study with a larger sample size.

## Conclusion

We revealed the survival benefits of IC + CCRT in patients with stage T3 and N2 NPC, while AC + CCRT improved LRRFS

 

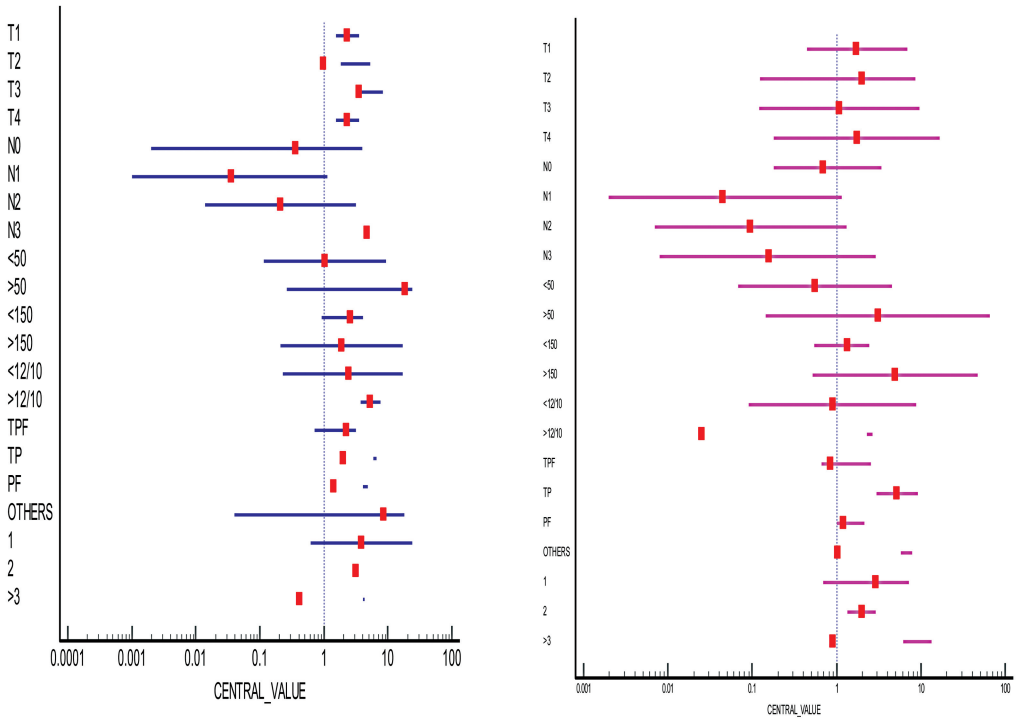


**Fig. 4** Forest plots depicting the HR and 95% CI for each subgroup analysis. The *squares* represent the HR, with 95% CI indicated by *horizontal bars*. AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; CRP, C-reactive protein; FFS, failure-free survival; HGB, hemoglobin; HR, hazard ratio; IC, induction chemotherapy; LDH, serum lactate dehydrogenase; M/F, male/female; OS, overall survival; P, cisplatin; PF, cisplatin and 5-florouracil; TP, docetaxel and cisplatin; TPF, docetaxel, cisplatin, and 5-florouracil.

in stage T4 NPC without any other survival advantage. Further research is needed to prove whether adding chemotherapy before rather than after CCRT should be recommended in LANPC, especially considering the possibility of adverse reaction.

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## Conflict of Interest

None declared.

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