Adjuvant chemotherapy following combined induction chemotherapy and concurrent chemoradiotherapy improves survival in N2–3-positive nasopharyngeal carcinoma patients

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Abstract

Objective This study aimed to explore the clinical value of adjuvant chemotherapy (ACT) following concurrent chemoradiotherapy (CCRT) and induction chemotherapy (ICT) in loco-regionally advanced nasopharyngeal carcinoma (LANC).

Methods We included 839 newly diagnosed LANC patients in this study. ICT plus CCRT (ICT + CCRT group) was administered to 443 patients, and 396 patients received ACT after ICT plus CCRT (ICT + CCRT + ACT group). Univariate and multivariate Cox regression analyses were carried out. Furthermore, propensity score matching (PSM) was applied to balance the study and control groups.

Results A total of 373 pairs of LANC patients were obtained after PSM analysis. We found that ACT following ICT + CCRT has no significant effect on improving the survival of LANC patients. By further exploring the ICT + CCRT + ACT treatment protocol, we excluded N0–1-positive patients and re-performed PSM in the ICT + CCRT and ICT + CCRT + ACT groups. Each group consisted of 237 patients. Kaplan–Meier analysis revealed that there were differences between the ICT + CCRT and ICT + CCRT + ACT groups in terms of the 5-year overall survival (OS) (78.9% vs. 85.0%, \(P = 0.034\)), disease-free survival (DFS) (73.4% vs. 81.7%, \(P = 0.029\)), and distant metastasis-free survival (DMFS) (84.9% vs. 76.0%, \(P = 0.019\)). In addition, the ICT + CCRT + ACT group had a higher incidence of grade 3/4 acute leukocytopenia/neutropenia.

Conclusion Compared with ICT + CCRT, ACT following ICT plus CCRT can reduce distant metastasis of N2–3-positive LANC and improve the OS and DFS. The results demonstrated the feasibility and clinical utility of ACT following ICT plus CCRT.

Keywords Concurrent chemo-radiotherapy · Nasopharyngeal carcinoma · Propensity score matching · Adjuvant chemotherapy · Induction chemotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is mainly distributed in southern China and countries in Southeast Asia and distant

metastasis is the leading cause of cancer mortality (Chen et al. 2019). Because of the nonspecific clinical symptoms and signs, so more than 60% of patients have locally advanced disease when diagnosed (Afqir et al. 2009). Because of its complicated anatomical position and high radiosensitivity, radiotherapy is the primary treatment for NPC. However, for locally advanced NPC patients (LANC), radiotherapy alone may have a limited treatment effect (Goto et al. 2013).

The result of the intergroup 0099 study demonstrated the clinical value of chemotherapy for patients with LANC (Al-Sarraf et al. 1998). Concurrent chemo-radiotherapy (CCRT) was found improve the survival and reduce the incidence of distant metastasis in LANC patients according to several prospective studies conducted in NPC epidemic regions (Chen et al. 2011; Lin et al. 2003). Subsequently, Sun et al. (Sun et al. 2016) found that compared to CCRT alone, the addition of induction chemotherapy (ICT) before CCRT can improve the 3-year failure-free survival (FFS) of LANC
patients. Thus, the National Comprehensive Cancer Network (NCCN) guidelines recommend CCRT following ICT as one of the best therapeutic regimens for LANC patients (category 2A) (NCCN 2021). ICT followed by definitive CCRT could improve clinical outcomes, but approximately 30% of patients will subsequently develop recurrence and/or distant metastasis (Chen et al. 2018; Hui et al. 2009; Li et al. 2019; Sun et al. 2016; Zhang et al. 2019).

Several studies have shown that adjuvant chemotherapy (ACT) following neoadjuvant therapy and surgery can markedly improve the local control and OS in non-small-cell lung carcinomas (Kwong et al. 2005; Rusch et al. 2007; White et al. 2021). In an individual patient data network meta-analysis of 5144 patients, ACT following CCRT achieved the best survival benefit (Ribassin-Majed et al. 2017). Zou et al. (2020) demonstrated the safety of ACT following ICT plus CCRT (ICT + CCRT + ACT) in LANC patients. However, they lack a head-to-head comparison between ICT + CCRT group and ICT + CCRT + ACT group. Therefore, the objective of this study was to further explore the efficacy of ICT plus CCRT followed by ACT in LANC patients.

**Patient selection and methods**

**Eligibility criteria**

Patients were re-staged using the AJCC/UICC 8th edition. The inclusion criteria were (1) WHO type I, II or III nasopharyngeal carcinoma; (2) completed the definitive intensity-modulated radiotherapy (IMRT); (3) Karnofsky performance status (KPS) ≥ 70; (4) AJCC stage III/IVa; and (5) received induction chemotherapy (ICT) with cisplatin/nedaplatin plus docetaxel (TP) followed by concurrent chemo-radiotherapy (CCRT) with or without TP adjuvant chemotherapy (ACT). The exclusion criteria were (1) a history of prior cancers and (2) signs of severe heart, lung, liver, renal, and other critical organ malfunction. If patients were confirmed tumor residual after treatment or identified as being a high risk of distant metastasis, the patients were recommended for ACT treatment. Adjuvant chemotherapy can kill viable residual tumor cells and has the potential to eliminate micro-metastases and improving systemic control. Patients with the following criteria were considered for ACT: (1) residual disease in the nasopharynx or cervical nodes was confirmed when 1 month after ICT + CCRT; (2) a KPS score of 70 or more after ICT + CCRT; (3) grade ≤ 2 gastrointestinal reactions, bone marrow suppression, oral mucositis or hematological toxicity during ICT + CCRT; and (4) no liver or kidney injury. Between January 2011 and December 2016, a total of 839 patients in our hospital were enrolled in this retrospective study and were divided into two groups: the ICT + CCRT group (N = 443) received TP induction chemotherapy followed by CCRT, and the ICT + CCRT + ACT group (N = 396) received TP induction chemotherapy plus CCRT followed by TP adjuvant chemotherapy. The study protocol was approved by the ethics committee of our hospital approved this retrospective investigation.

The details of this study are shown in Fig. 1.
### Induction chemotherapy

TP induction chemotherapy was administered to all patients. Cisplatin/nedaplatin (75–80 mg/m$^2$, day 1) and docetaxel (75 mg/m$^2$, day 1) were used in the TP regimen and this regimen was repeated every 3 weeks before CCRT.

### Concurrent chemo-radiotherapy

All patients underwent radical IMRT. We established target volumes based on the ICRU 62 study and defined the main cervical lymph node tumor volume (GTVnd) and gross tumor volume (GTVnx) of the whole macroscopic tumor as determined by magnetic resonance imaging (MRI), physical exams, and computed tomography (CT). The prescribed radiation dose was 68–74 Gy for GTVnx and 64–68 Gy for GTVnd in 31–35 fractions. Cisplatin/nedaplatin (75–80 mg/m$^2$, day 1) was administered to the ICT + CCRT + ACT and ICT + CCRT group patients every 3 weeks during radiotherapy.

### Adjuvant chemotherapy

Four weeks after completing CCRT, the ICT + CCRT + ACT group received cisplatin/nedaplatin (75–80 mg/m$^2$, day 1) and docetaxel (75 mg/m$^2$, day 1) every 3 weeks for 2–5 cycles.

### Data analysis

When completed the treatment, all patients were screened by physical examination, nasopharyngoscopy, and imaging every 3 months during the first 2 years after RT, 6 months during the next 3 years, and annually thereafter until death. OS was defined as the date from histological diagnosis to death or last follow-up. DMFS was defined as the date from histological diagnosis to first distant metastasis or last follow-up visit. LRFS was defined as the date from histological diagnosis to first loco-regional relapse or last follow-up visit. DFS was defined as the date from histological diagnosis to first treatment failure, death, or last follow-up visit. Version 4.0 of the Common Toxicity Criteria for Adverse Events (CTCAE 4.0) was utilized in the classification of toxicities related to treatment (CTC version 4.0).

The chi-square test or Fisher’s test was carried out to evaluate the differences in proportions of patients’ baseline characteristics and acute toxicity between the two groups. Parameters, such as the number of CCRT and ICT cycles, clinical stage, T stage, N stage, GTVnx, GTVnd, sex, age, and smoking, were used as co-variables in this study to eliminate potential confounding factors and balance the two groups of clinical characteristics (Austin 2013). In addition, we used R software (version 3.6.3) to carry out propensity score matching (PSM). Survival outcomes of the PSM cohorts in both groups were calculated using the Cox proportional hazards regression model and the Kaplan–Meier technique. Two-sided $P$ values of $<0.05$ were deemed statistically significant. Hazard ratios (HRs) and 95% confidence intervals (CIs) were recorded to indicate the prognostic value of the risk factors.

### Results

A total of 839 LANC patients were enrolled in this study and 443 patients were assigned in the ICT + CCRT group, and 396 were in the ICT + CCRT + ACT group. A total of 746 patients were enrolled in the study after PSM, with 373 patients per group. Table 1 summarizes the clinical characteristics.

The median follow-up time of 746 LANC patients was 74 months (3–127 months), and the 5-year OS, DFS, DMFS and LRFS rates were 82.9, 79.2%, 82.6% and 93.0%, respectively. The 5-year OS, DFS, DMFS and LRFS rates for the ICT + CCRT + ACT vs. ICT + CCRT + ACT group were 81.8% vs. 83.7% ($P$ = 0.315), 77.7% vs. 80.1% ($P$ = 0.389), 80.6% vs. 84.4% ($P$ = 0.185) and 92.4% vs. 93.1% ($P$ = 0.723), respectively (Table 2 and Fig. 2).

According to the univariate analysis results, the variables associated with a lower OS, DFS and DMFS were T stage, N stage and clinical stage (all $P < 0.05$). Compared to ICT + CCRT, ICT + CCRT + ACT failed to improve the 5-year OS (HR, 1.185; 95% CI 0.849–1.656; $P$ = 0.315), DFS (HR, 1.145; 95% CI 0.841–1.559; $P$ = 0.389), DMFS (HR, 1.257; 95% CI 0.895–1.766; $P$ = 0.185) or LRFS (HR, 1.104; 95% CI 0.640–1.903; $P$ = 0.723) (Table 2 and Fig. 2).

Multivariate analysis was performed to account for the numerous prognostic variables as indicated in Table 3. There were no significant changes between the ICT + CCRT and ICT + CCRT + ACT groups in OS, DFS, DMFS and LRFS rates. The HRs (95% CIs) of the ICT + CCRT group compared with the ICT + CCRT + ACT group were 1.185 (0.868–1.617), 1.146 (0.663–1.981), 1.299 (0.922–1.829) and 1.218 (0.870–1.705), respectively (all $P > 0.05$). Other independent prognostic factors were clinical stage and N stage (all $P < 0.05$).

Before PSM, 577 N2–3-positive patients were divided into two groups, with 301 patients in the ICT + CCRT group and 276 patients in the ICT + CCRT + ACT group. A total of 474 N2–3-positive patients were selected via PSM, with 237 patients per group. Table 4 lists the individual baseline characteristics.

The median follow-up time of these 474 patients was 74 months (3–127 months). In the univariate analysis, the 5-year OS, DFS, DMFS and LRFS rates for the ICT + CCRT vs. ICT + CCRT + ACT group were 73.4%...
vs. 81.7% ($P = 0.034$), 78.9% vs. 85.0% ($P = 0.029$), 76.0% vs. 84.9% ($P = 0.019$) and 90.8% vs. 94.7% ($P = 0.177$), respectively. In addition, patients with advanced N stage and clinical stage had a poorer 5-year OS, DFS and DMFS. Meanwhile, IC cycles improved the 5-year OS, DFS and DMFS (Table 5 and Fig. 3).

In the multivariate analysis, ACT following ICT plus CCRT significantly improved 5-year DMFS (HR: 1.724; 95% CI 1.123–2.648; $P = 0.013$), DFS (HR: 1.565; 95% CI 1.055–2.323; $P = 0.025$), LRFS (HR: 1.638; 95% CI 0.826–3.246; $P = 0.158$) and OS (HR: 1.064; 95% CI 1.059–2.430; $P = 0.026$). Clinical stage, N stage and ICT cycles were all independent variables for OS, DFS and DMFS (Table 4) (all $P < 0.05$) (see Table 6).

### Toxic effects

The comparisons of treatment-related toxicity of the ICT + CCRT and ICT + CCRT + ACT are presented in Table 5. There were no differences in the incidence of non-hematologic toxicities in this two groups (all $P > 0.05$). (all $P > 0.05$). Compared to ICT + CCRT, ICT + CCRT + ACT substantially increased the prevalence of grade 3/4

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Table 1 Patients’ characteristics in the ICT + CCRT and ICT + CCRT + ACT groups before and after PSM in LANC

| Item                  | Entire cohort (%) | ICT + CCRT | ICT + CCRT + ACT | $P$  | Propensity-score-matched cohort (%) | ICT + CCRT | ICT + CCRT + ACT | $P$  |
|-----------------------|-------------------|------------|------------------|------|-------------------------------------|------------|------------------|------|
| Total                 |                   | 443 (52.8) | 396 (47.2)       | 0.284| 373 (50.0)                          | 373 (50.0) |                  | 0.241|
| Age (y)               |                   |            |                  |      |                                     |            |                  |      |
| <46                   |                   | 204 (46.0) | 197 (49.7)       | 0.008|                                     | 168 (45.0) | 184 (49.3)       |      |
| ≥46                   |                   | 239 (54.0) | 199 (50.3)       |      |                                     | 205 (55.0) | 189 (50.7)       |      |
| Gender                |                   |            |                  |      |                                     |            |                  |      |
| Man                   |                   | 311 (70.2) | 310 (78.3)       | 0.508|                                     | 281 (75.3) | 287 (76.9)       | 0.668|
| Female                |                   | 132 (29.8) | 86 (21.7)        |      |                                     | 92 (24.7)  | 86 (23.1)        |      |
| T stage               |                   |            |                  |      |                                     |            |                  |      |
| T1–2                  |                   | 101 (22.8) | 98 (24.7)        | 0.585|                                     | 87 (23.3)  | 92 (24.7)        | 0.386|
| T3–4                  |                   | 342 (77.2) | 298 (53.3)       |      |                                     | 286 (76.7) | 281 (75.3)       |      |
| N stage               |                   |            |                  |      |                                     |            |                  |      |
| N0–1                  |                   | 142 (32.1) | 120 (30.3)       | 0.124|                                     | 123 (33.0) | 112 (30.0)       | 0.592|
| N2–3                  |                   | 301 (67.9) | 276 (69.7)       |      |                                     | 250 (67.0) | 261 (70.0)       |      |
| Clinical stage        |                   |            |                  |      |                                     |            |                  |      |
| III                   |                   | 302 (68.2) | 250 (63.1)       | 0.234|                                     | 245 (65.7) | 238 (63.8)       | 0.911|
| IV                    |                   | 141 (31.8) | 146 (36.9)       |      |                                     | 128 (34.3) | 135 (36.2)       |      |
| Smoking               |                   |            |                  |      |                                     |            |                  |      |
| No                    |                   | 257 (58.0) | 217 (54.8)       | 0.348|                                     | 176 (47.2) | 165 (44.2)       | 0.419|
| Yes                   |                   | 186 (42.0) | 179 (45.2)       |      |                                     | 197 (52.8) | 208 (55.8)       |      |
| CCRT cycles           |                   |            |                  |      |                                     |            |                  |      |
| <2                    |                   | 89 (20.1)  | 93 (23.5)        | 0.202|                                     | 89 (23.9)  | 87 (23.3)        | 0.385|
| ≥2                    |                   | 354 (79.9) | 303 (76.5)       |      |                                     | 284 (76.1) | 286 (76.7)       |      |
| IC cycles             |                   |            |                  |      |                                     |            |                  |      |
| <2                    |                   | 114 (25.7) | 87 (22.0)        | 0.327|                                     | 91 (24.4)  | 81 (21.7)        | 0.578|
| ≥2                    |                   | 329 (74.3) | 309 (78.0)       |      |                                     | 282 (75.6) | 292 (78.3)       |      |
| Dose of GTVnx (Gy)    |                   |            |                  |      |                                     |            |                  |      |
| <70                   |                   | 37 (8.4)   | 26 (6.6)         | 0.966|                                     | 30 (8.0)   | 26 (7.0)         | 0.610|
| ≥70                   |                   | 406 (91.6) | 370 (93.4)       |      |                                     | 343 (92.0) | 347 (93.0)       |      |
| Dose of GTVnd (Gy)    |                   |            |                  |      |                                     |            |                  |      |
| <66                   |                   | 70 (15.8)  | 63 (15.9)        | 1.000|                                     | 54 (14.5)  | 59 (15.8)        | 1.000|
| ≥66                   |                   | 373 (84.2) | 333 (84.1)       |      |                                     | 319 (85.5) | 314 (84.2)       |      |
| Histology             |                   |            |                  |      |                                     |            |                  |      |
| I                     |                   | 2 (0.4)    | 1 (0.6)          |      |                                     | 2 (0.5)    | 1 (0.3)          |      |
| II                    |                   | 10 (2.4)   | 9 (1.8)          |      |                                     | 9 (2.4)    | 9 (2.4)          |      |
| III                   |                   | 431 (97.2) | 386 (97.6)       |      |                                     | 362 (97.1) | 363 (97.3)       |      |
Table 2  Univariate analysis of prognostic factors in 746 patients with LANC

| Variable                                  | OS                  | DFS                  | DMFS                 | LRFS                 |
|-------------------------------------------|---------------------|----------------------|----------------------|----------------------|
|                                           | HR (95% CI)         | P                    | HR (95% CI)          | P                    | HR (95% CI)          | P                    |
| Group (ICT + CCRT vs. ICT + CCRT + ACT)   | 1.186 (0.849–1.656) | 0.315                | 1.145 (0.841–1.559)  | 0.389                | 1.257 (0.895–1.766)  | 0.185                | 1.104 (0.640–1.903)  | 0.723                |
| Gender (male vs. female)                  | 0.731 (0.480–1.113) | 0.144                | 0.749 (0.509–1.103)  | 0.144                | 0.689 (0.446–1.064)  | 0.093                | 0.927 (0.486–1.768)  | 0.818                |
| Age (<46 vs. ≥46)                         | 1.396 (0.993–1.961) | 0.055                | 1.199 (0.878–1.638)  | 0.252                | 1.257 (0.893–1.771)  | 0.190                | 1.237 (0.713–2.144)  | 0.449                |
| Smoking (yes vs. no)                      | 1.150 (0.825–1.604) | 0.410                | 1.142 (0.839–1.555)  | 0.397                | 1.144 (0.816–1.604)  | 0.434                | 1.543 (0.892–2.667)  | 0.121                |
| T stage (T1–2 vs. T3–4)                   | 1.440 (1.005–2.064) | 0.047                | 1.393 (1.021–1.952)  | 0.045                | 1.541 (1.073–2.214)  | 0.019                | 0.769 (0.386–1.532)  | 0.455                |
| N stage (N0–1 vs. N2–3)                   | 1.536 (1.039–2.271) | 0.031                | 1.480 (1.036–2.116)  | 0.031                | 1.691 (1.127–2.537)  | 0.011                | 1.432 (0.764–2.683)  | 0.262                |
| Clinical stage (III vs. IV)               | 2.103 (1.508–2.934) | <0.001               | 2.111 (1.551–2.872)  | <0.001               | 2.238 (1.632–3.209)  | <0.001               | 1.952 (1.133–3.362)  | 0.016                |
| IC cycles (<2 cycles vs. ≥2 cycles)       | 0.807 (0.556–1.171) | 0.259                | 0.889 (0.624–1.267)  | 0.514                | 0.762 (0.523–1.109)  | 0.155                | 2.344 (1.001–5.488)  | 0.050                |
| CCRT cycles (<2 cycles vs. ≥2 cycles)     | 0.931 (0.634–1.365) | 0.713                | 0.873 (0.614–1.240)  | 0.448                | 0.874 (0.595–1.284)  | 0.492                | 1.164 (0.598–2.264)  | 0.655                |
| Dose of GTVnx (<70 Gy vs. ≥70 Gy)         | 0.913 (0.493–1.690) | 0.771                | 1.016 (0.564–1.830)  | 0.957                | 1.140 (0.580–2.242)  | 0.704                | 0.508 (0.229–1.127)  | 0.096                |
| Dose of GTVnd (<66 Gy vs. ≥66 Gy)         | 0.942 (0.602–1.474) | 0.793                | 1.079 (0.700–1.665)  | 0.731                | 1.133 (0.698–1.841)  | 0.613                | 0.902 (0.440–1.850)  | 0.778                |

Fig. 2  Kaplan–Meier analysis of overall survival, disease-free survival, distant metastasis-free survival and Loco-regional relapse-free survival curves for the 746 patients with LANC.

leukocytopenia \( (P < 0.001) \) and neutropenia \( (P < 0.001) \) (see Table 7).

**Discussion**

To the best of our knowledge, this is the first study to examine the clinical effectiveness of ICT + CCRT followed by ACT in LANC patients. We discovered that ACT following ICT + CCRT could not improve OS, DMFS, LRFS or DFS in LANC patients. Meanwhile, we found that patients with N2–3-positive in the ICT + CCRT + ACT group had a better 5-year OS, DFS and DMFS than those in the ICT + CCRT group. Based on the result this study, we suggest that patients with N2–3-positive LANC should be treated with the ICT + CCRT + ACT treatment protocol to further reduce the incidence of distant metastasis.

CCRT is the cornerstone of the treatment of LANC (Chan et al. 2005; Lin et al. 2003). IMRT has been widely used in NPC and significantly improved the local control rates. However, distant metastasis remains the main cause of treatment failure (Sun et al. 2014; Tang et al. 2013). In
Recent years, the combination of ICT or ACT with CCRT has minimized the incidence of distant metastases in LANC patients (Chen et al. 2021a; b). Compared with CCRT alone, CCRT following ICT was found to improve the 5-year OS in an IPD pooled analysis (HR = 0.75, 95% CI 0.57–0.99) by improving DMFS (HR = 0.68, 95% CI 0.90–0.51) (Chen et al. 2018). Since then, ICT + CCRT has become the standard treatment for LANC according to the NCCN guidelines (NCCN 2021). Although the addition of ICT to CCRT improved the survival of LANC patients, there were still some patients with high risk might suffer a tumor residual in primary site and lymph node after treatment. ACT is administered to reduce residual tumor cells, prevent relapse and eliminate micro-metastases (Song et al. 2013) and actually in the NCCN guidelines, the ICT + CCRT and CCRT + ACT regimens had the same level of evidence and both were category 2A (NCCN 2021). Therefore, whether ACT following ICT plus CCRT can improve survival in LANC patients with high-risk is worthy of further exploration.

In fact, ACT remains a controversial treatment because previous study failed to demonstrate clinical effectiveness (Chen et al. 2012; Chen et al. 2017; Chan et al. 2018). Chen et al. showed that there were no differences between the CCRT group and the CCRT + ACT group in 5-year FFS (75% vs. 71%; P = 0.45), OS (83% vs. 80%; P = 0.35), DMFS (85% vs. 80%; P = 0.30) and LRFS (91% vs. 90%; P = 0.73) and the main reason was the poor compliance in ACT after CCRT group. Approximately 40% of patients did not complete three cycles of ACT, and 44 of them refused ACT (Chen et al. 2012, 2017). In our study, all the patients in the ICT + CCRT + ACT group received two or more courses of ACT, which makes the results more reliable.

Notably, not all patients can benefit from ACT. Patients who are more likely to benefit from ACT are still uncertain at present. In Chen et al.’s study, they included many N0–1-positive patients, which makes the negative results in CCRT + ACT group in some degree (Chen et al. 2012, 2017). In Chan et al.’s study (2018), they explored the connection between ACT and plasma Epstein-Barr virus DNA and found that ACT with cisplatin and gemcitabine (GP) could not improve the 5-year DMFS. Therefore, biomarkers cannot be used to screen patients who can benefit from ACT. Our findings indicate that the ICT + CCRT + ACT treatment protocol could further improve the OS, DFS and DMFS in N2–3-positive LANC patients. The 5-year OS, DFS and DMFS rates in the ICT + CCRT group were 78.9%, 73.4% and 63.7%, respectively, which makes the negative results in CCRT + ACT group in some degree (Chen et al. 2012, 2017). In Chan et al.’s study (2018), they explored the connection between ACT and plasma Epstein-Barr virus DNA and found that ACT with cisplatin and gemcitabine (GP) could not improve the 5-year DMFS. Therefore, biomarkers cannot be used to screen patients who can benefit from ACT. Our findings indicate that the ICT + CCRT + ACT treatment protocol could further improve the OS, DFS and DMFS in N2–3-positive LANC patients. The 5-year OS, DFS and DMFS rates in the ICT + CCRT group were 78.9%, 73.4% and 63.7%, respectively, which makes the negative results in CCRT + ACT group in some degree (Chen et al. 2012, 2017).

| Variable                  | OS HR (95% CI) | DFS HR (95% CI) | DMFS HR (95% CI) | LRFS HR (95% CI) |
|---------------------------|----------------|-----------------|-----------------|-----------------|
| Group (ICT + CCRT vs. ICT + CCRT + ACT) | 1.218 (0.870–1.705) | 0.251 | 1.185 (0.868–1.617) | 0.285 | 1.299 (0.922–1.289) | 0.135 | 1.146 (0.663–1.981) | 0.609 |
| Gender (male vs. female) | 0.710 (0.473–1.106) | 0.159 | 0.732 (0.471–1.138) | 0.166 | 0.650 (0.398–1.061) | 0.081 | 1.287 (0.577–2.871) | 0.609 |
| Age (<46 vs ≥ 46)        | 1.377 (0.976–1.941) | 0.068 | 1.183 (0.858–1.630) | 0.306 | 1.214 (0.852–1.729) | 0.283 | 1.223 (0.696–2.151) | 0.484 |
| Smoking (yes vs. no)     | 0.967 (0.658–1.420) | 0.864 | 1.003 (0.702–1.433) | 0.988 | 0.959 (0.651–1.412) | 0.831 | 1.631 (0.817–3.255) | 0.165 |
| T stage (T1–2 vs. T3–4)  | 1.302 (0.849–1.994) | 0.226 | 1.253 (0.849–1.848) | 0.256 | 1.408 (0.906–2.187) | 0.128 | 1.379 (0.710–2.679) | 0.343 |
| N stage (N0–1 Vs. N2–3) | 1.595 (1.072–2.400) | 0.023 | 1.576 (1.080–2.302) | 0.018 | 1.738 (1.157–2.612) | 0.007 | 0.814 (0.390–1.700) | 0.584 |
| Clinical stage (III vs. IV) | 2.373 (1.677–3.357) | <0.001 | 2.346 (1.700–3.238) | <0.001 | 2.642 (1.852–3.768) | <0.001 | 1.829 (1.044–3.205) | 0.025 |
| IC cycles (<2 cycles vs. ≥ 2 cycles) | 0.758 (0.518–1.110) | 0.154 | 0.820 (0.571–1.176) | 0.281 | 0.694 (0.473–1.019) | 0.062 | 2.261 (0.960–5.327) | 0.072 |
| CCRT cycles (<2 cycles vs. ≥ 2 cycles) | 0.921(0.624–1.358) | 0.677 | 0.861(0.603–1.231) | 0.412 | 0.840(0.568–1.241) | 0.381 | 1.271(0.649–2.491) | 0.484 |
| Dose of GTVnx (<70 Gy vs. ≥ 70 Gy) | 0.848 (0.456–1.577) | 0.603 | 0.939 (0.519–1.696) | 0.834 | 1.057 (0.536–2.087) | 0.872 | 0.501 (0.222–1.131) | 0.096 |
| Dose of GTVnd (<66 Gy vs. ≥ 66 Gy) | 0.966 (0.616–1.514) | 0.880 | 1.106 (0.715–1.710) | 0.650 | 1.163 (0.714–1.984) | 0.544 | 0.933 (0.453–1.924) | 0.852 |
of apoptosis (Kim et al. 2012). Meanwhile, docetaxel has been demonstrated a lower rate of grade 3 and 4 nausea/vomiting than fluorouracil. A retrospective study revealed that compared with the TP regimen, 5-fluorouracil-based ICT significantly increased the incidence of mucositis/vomiting toxicity (He et al. 2019). Zhang et al. (2016) also discovered that ACT with TP is a successful therapeutic regimen for LANC patients, with no patients experiencing grade 3/4 nausea or vomiting. Therefore, LANC patients seemed present a better tolerance in the TP regimen than PF regimen.

According to Zou et al., the rate of grade 3/4 leukocytopenia and neutropenia was significantly elevated and the incidence was 67.5% and 55.8%, respectively, which was similar to the result of our study Zou et al. (2020). We found that grade 3/4 leukocytopenia/neutropenia in the ICT + CCRT + ACT group was significantly greater than that in the ICT + CCRT group (all $P < 0.001$). In addition, our study showed no differences in 3/4 nausea/vomiting and oral mucositis between the two groups, which was in line with Zhang et al.’s research (Zhang et al. 2016).

There are some limitations in our study. First, this is a retrospective study and the data was collected from a single center, which makes some biases were inevitable. PSM can help to minimize the confounding effects, but other unmeasured potential confounding factors may still exist. Another

### Table 4 Characteristics of the N2–3-positive LANC patients in the ICT + CCRT and ICT + CCRT + ACT groups before and after PSM

| Item                | Entire cohort (%) | ICT + CCRT | ICT + CCRT + ACT | $P$ | ICT + CCRT | ICT + CCRT + ACT | $P$ |
|---------------------|-------------------|------------|------------------|-----|------------|------------------|-----|
| Total               | 301 (52.2)        | 276 (47.8) | 237 (50.0)       | 0.167 | 237 (50.0) |                  |     |
| Age                 |                   |            |                  |     |            |                  |     |
| < 46                | 147 (48.8)        | 142 (51.4) | 135 (57.0)       | 120 (50.6) | 102 (43.0) | 117 (49.9)       |     |
| ≥ 46                | 154 (51.2)        | 134 (48.6) | 102 (43.0)       | 117 (49.9) | 102 (43.0) | 117 (49.9)       |     |
| Gender              |                   |            |                  |     |            |                  |     |
| Man                 | 210 (79.4)        | 213 (71.3) | 178 (75.1)       | 177 (74.7) | 178 (75.1) | 177 (74.7)       |     |
| Female              | 91 (20.6)         | 63 (28.7)  | 59 (24.9)        | 60 (25.3)  | 59 (24.9) | 60 (25.3)        |     |
| T stage             |                   |            |                  |     |            |                  |     |
| T1–2                | 99 (32.9)         | 98 (35.5)  | 81 (34.2)        | 94 (39.7)  | 81 (34.2) | 94 (39.7)        |     |
| T3–4                | 202 (67.1)        | 178 (64.5) | 156 (65.8)       | 143 (60.3) | 156 (65.8) | 143 (60.3)       |     |
| N stage             |                   |            |                  |     |            |                  |     |
| N 2                 | 235 (78.1)        | 224 (81.2) | 187 (78.9)       | 188 (79.3) | 187 (78.9) | 188 (79.3)       |     |
| N 3                 | 66 (21.9)         | 52 (18.8)  | 50 (21.1)        | 49 (20.7)  | 50 (21.1) | 49 (20.7)        |     |
| Clinical stage      |                   |            |                  |     |            |                  |     |
| III                 | 197 (65.4)        | 171 (62.0) | 156 (65.8)       | 162 (68.4) | 156 (65.8) | 162 (68.4)       |     |
| IV                  | 104 (34.6)        | 105 (38.0) | 81 (34.2)        | 75 (31.6) | 81 (34.2) | 75 (31.6)        |     |
| Smoking             |                   |            |                  |     |            |                  |     |
| No                  | 170 (56.5)        | 144 (52.2) | 132 (55.7)       | 127 (53.6) | 132 (55.7) | 127 (53.6)       |     |
| Yes                 | 131 (43.5)        | 132 (47.8) | 105 (44.3)       | 110 (46.4) | 105 (44.3) | 110 (46.4)       |     |
| CCRT cycles         |                   |            |                  |     |            |                  |     |
| < 2                 | 66 (21.9)         | 65 (23.6)  | 58 (24.5)        | 52 (21.9)  | 58 (24.5) | 52 (21.9)        |     |
| ≥ 2                 | 235 (78.1)        | 211 (76.4) | 179 (75.5)       | 185 (78.1) | 179 (75.5) | 185 (78.1)       |     |
| IC cycles           |                   |            |                  |     |            |                  |     |
| < 2                 | 70 (23.3)         | 57 (20.7)  | 60 (25.3)        | 49 (20.7)  | 60 (25.3) | 49 (20.7)        |     |
| ≥ 2                 | 231 (76.7)        | 219 (79.3) | 177 (74.7)       | 188 (79.3) | 177 (74.7) | 188 (79.3)       |     |
| Dose of GTVnx       |                   |            |                  |     |            |                  |     |
| < 70                | 24 (8.0)          | 17 (6.2)   | 16 (6.8)         | 15 (6.3)  | 16 (6.8) | 15 (6.3)         |     |
| ≥ 70                | 277 (92.0)        | 259 (93.8) | 221 (93.2)       | 222 (93.7) | 221 (93.2) | 222 (93.7)       |     |
| Dose of GTVnd       |                   |            |                  |     |            |                  |     |
| < 66                | 46 (15.3)         | 44 (15.9)  | 38 (16.0)        | 37 (15.6) | 38 (16.0) | 37 (15.6)        |     |
| ≥ 66                | 255 (84.7)        | 232 (84.1) | 199 (84.0)       | 200 (84.4) | 199 (84.0) | 200 (84.4)       |     |
| Histology           |                   |            |                  |     |            |                  |     |
| I                   | 1 (0.3)           | 1 (0.4)    | 1 (0.4)          | 1 (0.4)   | 1 (0.4) | 1 (0.4)          |     |
| II                  | 6 (2.0)           | 7 (2.5)    | 5 (2.1)          | 7 (3.0)   | 5 (2.1) | 7 (3.0)          |     |
| III                 | 294 (97.7)        | 268 (97.1) | 231 (97.5)       | 229 (96.6) | 231 (97.5) | 229 (96.6)       |     |
**Table 5** Univariate analysis of prognostic factors in 474 patients with N2–3-positive LANC

| Variable                                      | OS HR (95% CI) | DFS HR (95% CI) | DMFS HR (95% CI) | LRRFS HR (95% CI) |
|-----------------------------------------------|----------------|-----------------|------------------|-------------------|
| **Group (ICT + CCRT Vs. ICT + CCRT + ACT)**   | 1.548 (1.029–2.327) | 0.034 1.532 (1.039–2.258) | 0.029 1.638 (1.077–2.490) | 0.019 1.587 (0.806–3.124) |
| **Gender (male vs. female)**                  | 0.677 (0.410–1.119) | 0.128 0.702 (0.435–1.132) | 0.147 0.659 (0.377–1.082) | 0.095 0.964 (0.452–2.058) |
| **Age (< 46 vs. ≥ 46)**                      | 1.169 (0.784–1.744) | 0.444 1.050 (0.718–1.538) | 0.800 1.144 (0.760–1.722) | 0.518 1.097 (0.565–2.129) |
| **Smoking (yes vs. no)**                     | 1.268 (0.850–1.891) | 0.245 1.379 (0.932–1.996) | 0.111 1.271 (0.844–1.913) | 0.250 1.897 (0.965–3.731) |
| **T stage (T1–2 vs. T3–4)**                  | 1.247 (0.831–1.869) | 0.286 1.182 (0.802–1.743) | 0.397 1.327 (0.879–2.004) | 0.179 0.567 (0.265–1.212) |
| **N stage (N0–1 vs. N2–3)**                  | 2.613 (1.732–3.942) | <0.001 2.415 (1.623–3.592) | <0.001 3.077 (2.031–4.661) | <0.001 1.014 (0.443–2.322) |
| **Clinical stage (III vs. IV)**               | 2.809 (1.878–4.202) | <0.001 2.581 (1.762–3.781) | <0.001 3.307 (2.183–5.009) | <0.001 1.497 (0.761–2.947) |
| **IC cycles (< 2 cycles vs. ≥ 2 cycles)**     | 0.659 (0.428–0.940) | 0.043 0.659 (0.437–0.994) | 0.040 0.641 (0.413–0.996) | 0.036 0.755 (0.363–1.573) |
| **CCRT cycles (< 2 cycles vs. ≥ 2 cycles)**   | 1.050 (0.652–1.691) | 0.840 1.102 (0.694–1.748) | 0.681 1.095 (0.667–1.798) | 0.718 1.266 (0.553–2.999) |
| **Dose of GTVnx (< 70 Gy vs. ≥ 70 Gy)**       | 0.600 (0.302–1.192) | 0.145 0.728 (0.368–1.441) | 0.362 0.820 (0.379–1.772) | 0.613 0.681 (0.208–2.275) |
| **Dose of GTVnd (< 66 Gy vs. ≥ 66 Gy)**       | 0.964 (0.562–1.644) | 0.885 1.101 (0.647–1.873) | 0.724 1.079 (0.611–1.906) | 0.794 2.108 (0.646–6.886) |

Caveat is that some information of outpatient was unable to be fully documented. Therefore, large prospective clinical studies will be required to confirm our results.

**Conclusion**

In summary, our research revealed that there were no differences in the OS, DFS, DMFS and LRRFS between the ICT + CCRT and ICT + CCRT + ACT of LANC patients. When we excluded N0–1-positive patients and performed PSM in the ICT + CCRT and ICT + CCRT + ACT groups, we found that the ICT + CCRT + ACT treatment protocol could improve DMFS in N2–3-positive LANC patients and prolong the OS. Moreover, adding ACT after ICT plus CCRT increased the incidence of adverse effects, such as grade 3/4 leukocytopenia and neutropenia, but these toxic events are controllable in clinic practice. Our study proved the efficacy and feasibility of the ICT + CCRT + ACT treatment protocol, so we recommend the ICT + CCRT + ACT treatment protocol.
treatment protocol as a preferred treatment for N2–3-positive LANC patients.

Author contributions R-HZ, Y-WY and H-YT conceived the study. HL, C-XH, RL, FH and H-YT collected all clinical data. H-YT and RL performed the statistical analyses. H-YT and K-PD prepared and edited the manuscript. All authors read and approved the final manuscript. Fang He has made contributions to the English language revision of this paper and put forward valuable modification comments.

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Declarations

Conflict of interest The authors declare they have no competing interests.

Ethics approval This retrospective study was approved by the Institutional Review Board (IRB) of the Affiliated Cancer Hospital & Institute of Guangzhou Medical University. Patients were required to provide written informed consent before enrolling in the study.

Table 6 Multivariate analyses of prognostic factors in 474 patients with N2–3-positive LANC

| Variable | OS | DFS | DMFS | LRRFS |
|----------|----|-----|------|-------|
| Group (ICT + CCRT Vs. ICT + CCRT + ACT) | 1.619 (1.067–2.456) | 0.023 | 1.565 (1.055–2.323) | 0.025 | 1.724 (1.123–2.648) | 0.013 | 1.638 (0.826–3.246) | 0.158 |
| Gender (male vs. female) | 0.735 (0.413–1.307) | 0.294 | 0.834 (0.478–1.454) | 0.522 | 0.700 (0.385–1.273) | 0.243 | 1.963 (0.716–5.935) | 0.212 |
| Age (<46 vs. ≥46) | 1.036 (0.682–1.575) | 0.867 | 0.884 (0.591–1.321) | 0.547 | 0.947 (0.615–1.459) | 0.806 | 0.961 (0.479–1.929) | 0.911 |
| Smoking (yes vs. no) | 1.181 (0.734–1.901) | 0.492 | 1.379 (0.873–2.179) | 0.168 | 1.211 (0.751–1.953) | 0.433 | 2.700 (1.035–7.041) | 0.042 |
| T stage (T1–2 vs. T3–4) | 1.102 (0.598–2.031) | 0.755 | 1.076 (0.602–1.924) | 0.805 | 1.135 (0.614–2.099) | 0.685 | 0.572 (0.199–1.642) | 0.299 |
| N stage (N0–1 vs. N2–3) | 1.937 (1.214–3.091) | 0.006 | 1.852 (1.189–2.883) | 0.006 | 2.290 (1.415–3.703) | 0.001 | 0.750 (0.330–1.701) | 0.491 |
| Clinical stage (II vs. IV) | 3.281 (1.783–6.384) | <0.001 | 3.078 (1.697–5.757) | <0.001 | 4.057 (2.102–7.833) | <0.001 | 1.954 (0.791–4.828) | 0.147 |
| IC cycles (<2 cycles vs. ≥2 cycles) | 0.608 (0.388–0.953) | 0.030 | 0.609 (0.396–0.934) | 0.023 | 0.592 (0.374–0.937) | 0.025 | 0.838 (0.391–1.793) | 0.594 |
| CCRT cycles (<2 cycles vs. ≥2 cycles) | 1.006 (0.619–1.635) | 0.980 | 1.048 (0.653–1.684) | 0.845 | 1.026 (0.618–1.704) | 0.921 | 1.336 (0.569–3.136) | 0.572 |
| Dose of GTVnx (<70 Gy vs. ≥70 Gy) | 0.663 (0.329–1.337) | 0.251 | 0.787 (0.392–1.577) | 0.499 | 0.922 (0.420–2.024) | 0.839 | 0.730 (0.220–2.423) | 0.607 |
| Dose of GTVnd (<66 Gy vs. ≥66 Gy) | 1.064 (0.615–1.838) | 0.825 | 1.226 (0.713–2.109) | 0.461 | 1.251 (0.699–2.237) | 0.451 | 2.052 (0.621–6.783) | 0.239 |

Table 7 Adverse events after propensity score matching in patients with LANC after propensity score matching in patients with N2–3-positive LANC

| Adverse event | ICT + CCRT (case%) | ICT + CCRT + ACT (case%) | P-value | ICT + CCRT (case%) | ICT + CCRT + ACT (case%) | P-value |
|----------------|--------------------|--------------------------|---------|--------------------|--------------------------|---------|
| Leukocytopenia  | Grade 0–2 (285/367) | Grade 0–2 (168/233) | <0.001 | Grade 0–2 (131/189) | Grade 0–2 (106/166) | <0.001 |
| Neutropenia     | Grade 0–2 (294/365) | Grade 0–2 (182/292) | <0.001 | Grade 0–2 (153/216) | Grade 0–2 (84/105) | 0.003 |
| Thrombocytopenia| Grade 0–2 (358/373) | Grade 0–2 (227/268) | 0.700 | Grade 0–2 (232/294) | Grade 0–2 (5/23) | 0.294 |
| Anemia          | Grade 0–2 (355/355) | Grade 0–2 (222/222) | 0.516 | Grade 0–2 (225/225) | Grade 0–2 (12/12) | 0.552 |
| Non-Hematologic | Grade 0–2 (367/373) | Grade 0–2 (233/233) | 0.761 | Grade 0–2 (235/235) | Grade 0–2 (2/2) | 0.686 |
| Liver function  | Grade 0–2 (373/373) | Grade 0–2 (237/237) | 1.000 | Grade 0–2 (237/237) | Grade 0–2 (0/0) | 1.000 |
| Renal function  | Grade 0–2 (290/373) | Grade 0–2 (186/233) | 0.368 | Grade 0–2 (188/233) | Grade 0–2 (49/23) | 0.192 |
| Oral mucositis  | Grade 0–2 (352/352) | Grade 0–2 (224/224) | 0.745 | Grade 0–2 (229/229) | Grade 0–2 (8/8) | 0.264 |
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