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Docetaxel and cisplatin induction chemotherapy with or without fluorouracil in locoregionally advanced nasopharyngeal carcinoma: A retrospective propensity score matching analysis

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Abstract

Purpose: To investigate whether the addition of fluorouracil to docetaxel and cisplatin induction chemotherapy (IC) can truly improve the prognosis of patients with locoregionally advanced nasopharyngeal carcinoma (NPC).

Methods: A total of 801 patients newly diagnosed with non-metastatic locoregionally advanced NPC were included as the subjects. In this study, propensity score matching (PSM) was used for analysis of overall survival (OS), distant metastasis-free survival (DMFS), progression-free survival (PFS) and locoregional relapse-free survival (LRRFS), and the chi-squared test or Fisher's exact test was used to investigate toxic reactions.

Results: Patients received treatment with docetaxel and cisplatin (TP) or docetaxel, cisplatin and fluorouracil (TPF). With a median follow-up time of 60 months (range: 5–124 months), the TPF group had better 5-year OS (84.7% *vs* 79.0%; $P = 0.037$), PFS (84.6% *vs* 76.8%; $P = 0.008$) and DMFS (89.5% *vs* 82.3%; $P = 0.004$) than the TP group. After PSM, 258 patients were matched in each cohort. The Kaplan–Meier analysis showed that the 5-year OS, PFS and DMFS were 85.5%, 84.2% and 89.2%, respectively, in the TPF group, higher than the 80.8%, 75.0% and 81.4%, respectively, in the TP group ($P = 0.048$, 0.009 and 0.006, respectively). Moreover, the multivariate analysis revealed that different IC regimens were independent prognostic factors for PFS and DMFS ($P = 0.014$ and 0.010, respectively).

Conclusion: This study found that compared with the TP regimen, TPF induction chemotherapy is associated with improved survival in patients with locoregionally advanced NPC. TPF can produce more mucosal and nausea/vomiting adverse reactions than TP.

KEYWORDS
fluorouracil, induction chemotherapy, nasopharyngeal carcinoma, propensity score-matching

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC), one of the most common malignant tumors in the head and neck, occurs frequently in South China and mostly in Guangdong Province, where the rates are between 20 and 30 per 100,000 people.[1] Concurrent chemoradiotherapy (CCRT) is the current standard regimen for patients with locoregionally advanced NPC.[2] In the era of intensity-modulated radiotherapy (IMRT), local control has improved; however, the distant metastasis rate still reaches 15–20%, and this has become the major cause of treatment failure.[3] Therefore, based on CCRT, finding a way to reduce distant metastasis has become a major challenge in treating locoregionally advanced NPC, and adjuvant chemotherapy (AC) and induction chemotherapy (IC) have become the areas of research interest. Some studies in recent years have shown that IC has better compliance than AC in terms of the advantage of early clearance of micrometastatic foci; CCRT combined with AC (CCRT+AC) produces more obvious side effects than IC combined with CCRT (IC+CCRT).[4,5] Recent studies have shown that IC+CCRT can improve DMFS, progression-free survival (PFS) and OS.[6–8] Therefore, it has become a new way to improve the survival outcomes of NPC patients. After the national comprehensive cancer network (NCCN) upgraded IC from category 2B to category 2A in 2018,[9] IC+CCRT has become a standard model for locoregionally advanced NPC.

In terms of choosing an appropriate IC regimen, the study of Chen et al[7] showed that compared with other IC regimens, taxane, cisplatin, and fluorouracil)TPF(+CCRT significantly improved the OS and PFS of patients with locoregionally advanced NPC. After these findings were adopted by the NCCN Guidelines, TPF has become the mainstream regimen for NPC induction chemotherapy. However, the optimal IC regimen remains to be further explored.

Notably, some findings in recent years have shown that TPF, the triple-drug IC regimen, can produce stronger oromucosal and gastrointestinal reactions than other double-drug IC regimens followed by CCRT.[7,8] However, whether the double-drug IC regimen of TP can replace the triple-drug regimen of TPF remains unknown, and our attention has focused on the cisplatin and fluorouracil (PF) and docetaxel plus cisplatin (TP) regimens. The findings[10] indicate that the clinical outcomes of TPF induction chemotherapy were improved over those of PF. Hui et al[11] conducted a phase II clinical study and found that TP-induced chemotherapy followed by CCRT could significantly improve the overall survival rate (HR = 0.24; 95% CI, 0.078–0.73). However, randomized clinical studies on head-to-head comparisons of TP with TPF are lacking. Therefore, we used propensity score matching to analyze retrospectively a large cohort of NPC patients treated with TP or TPF to explore whether TP could be an alternative to TPF as an IC regimen for locoregionally advanced NPC.

2 | PATIENT SELECTION AND METHODS

2.1 | Patient selection

Screening eligibility criteria: patients diagnosed pathologically with NPC, clinical stage III–IVa (according to the 8th edition of the UICC/AJCC staging system) who completed IC followed by CCRT (with RT given as IMRT); performance status scores of 0–1. Exclusion criteria were: (1) patients with distant metastasis; (2) patients complicated with other malignant tumors, (3) patients with severe heart, lung, liver, kidney and other key organ dysfunction that may not tolerate treatment, (4) patients who were pregnant or lactating and (5) dropout patients or patients with incomplete clinical data. From May 2009 to December 2016, at the Affiliated Cancer Hospital & Institute of Guangzhou Medical University, 1518 patients with NPC met the above screening criteria. Then, 426 patients who received other induction chemotherapy regimens and 291 patients who underwent AC following CCRT were excluded. Ultimately, 801 patients were included as subjects for analysis (of which 536 received TP and 265 received TPF). Details are shown in Figure 1.

2.2 | Patient data

All data were collected from the hospital information system and paper medical records, including age, gender, pathological diagnosis, date of diagnosis, imaging results, smoking history, chemotherapeutic modalities and agents, radiotherapy technique and dosage and follow-ups. All patients were restaged according to the 8th edition AJCC/UICC staging manuals. The T and N categories depended on magnetic resonance imaging (MRI) and computed tomography (CT). In this study, abdominal B-mode ultrasound (B-US), chest digital radiography (DR), CT and emission computed tomography (ECT) for systemic bone scans were used to exclude systemic metastasis, and a systemic PET-CT scan was also performed for some patients.

2.3 | Induction chemotherapy

IC was performed in the TPF and TP groups. Patients in the TPF group were infused with docetaxel (60 mg/mš) + cisplatin (60 mg/mš) + fluorouracil (600 mg/mš, 24 consecutive hours daily for 5 days or 1000 mg/mš, 24 consecutive hours daily for 3 days), whereas patients in the TP group received cisplatin (80–75 mg/mš) combined with docetaxel (75 mg/mš). Both regimens were repeated every 3 weeks in the intended treatment cycle of two to four based on treatment effect.

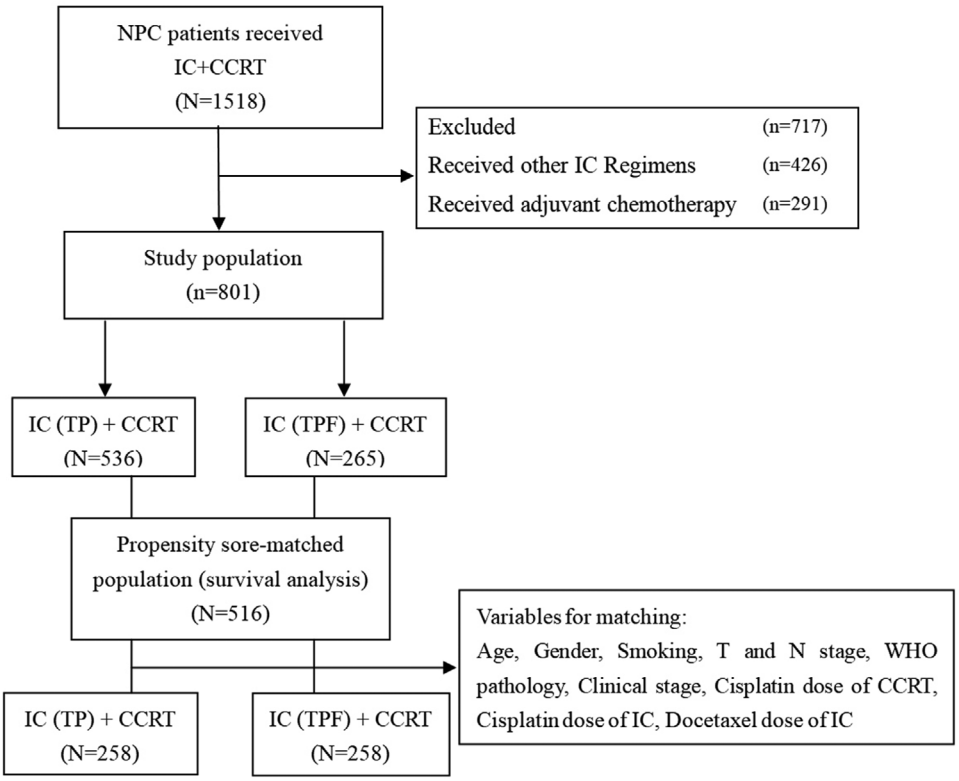

FIGURE 1 Flow diagram. IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; TP, cisplatin and docetaxel; TPF, docetaxel, cisplatin and fluorouracil

2.4 | CCRT

All patients in this study received radical IMRT. The prescribed doses were 70 Gy for the gross tumor volume (GTV) and 66–68 Gy for cervical lymph node involvement (GTVnd) five times a week for 6–7 weeks. Overall dose fluctuations were within 5%. All patients received one to three courses of cisplatin concurrent chemotherapy (80 mg/mš) every 3 weeks during radiotherapy.

2.5 | Data analysis

The follow-up time was calculated from the date of diagnosis. At the end of treatment, follow-up visits were made every 3 months in 3 years, every 6 months in 4–5 years and once every year after 5 years. This study aimed to assess OS, PFS, DMFS and LRRFS, which are defined as the time from diagnosis to death for any cause, first disease progression, first distant metastasis and first local-regional recurrence. Adverse events during treatment were graded according to the National Cancer Institute (NCCN) Common Terminology Criteria for Adverse Events version 4.0.

Adverse events and clinical characteristics of both groups were analyzed using the chi-squared test or Fisher's exact test with SPSS 25.0 software. The survival outcomes of the original unmatched cohort and the propensity score-matched (PSM) cohort were calculated using the Kaplan-Meier method. Based on the calculated results, the survival curves were plotted for two groups. Cox regression was used for multivariate analysis with the analytical variables including T stage, N stage, clinical staging, gender, age, smoking history, cisplatin dose of CCRT, cisplatin dose of IC, docetaxel dose of IC and IC regimen. For all analyses, the results were considered statistically significant at $P < 0.05$. All the test results demonstrated a significant bilateral difference, and the results of multivariable analyses were presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

The PSM method was used to reduce the effect of confounding factors and to make the comparison between the study and control groups more reasonable.[12] PSM treatment outcomes were evaluated by calculating covariates that predict treatment response. The covariates in this study included gender, age (≤47/ > 47 years), smoking history (yes/no), T stage, N stage, clinical staging, cisplatin dose of CCRT, cisplatin dose of IC, docetaxel dose of IC and pathological classification. PSM was conducted using SPSS 25.0 by matching 516 cases, with the matching volume taken as 0.01.

3 | RESULTS

Of 801 patients, there were 536 in the TP group and 265 in the TPF group. Patients receiving TP treatment ($n = 258$) and patients receiving TPF treatment ($n = 258$) were paired at 1:1 after PSM. The specific baseline characteristics are shown in Table 1.

TABLE 1 The differences in patient characteristics between the TPF and TP groups before and after propensity matching

	Entire cohort (%)			Propensity-score matched cohort (%)		
Item	TPF	TP	*P*	TPF	TP	*P*
Total	265 (33.1)	536 (66.9)		258 (50.0)	258 (50.0)	
Age			0.210			0.791
≤47	142 (53.6)	262 (48.9)		138 (53.4)	135 (53.1)	
>47	123 (46.4)	274 (51.1)		120 (46.5)	123 (46.9)	
Gender			0.095			0.235
Male	205 (77.4)	385 (71.8)		198 (76.7)	209 (81.1)	
Female	60 (22.6)	151 (28.2)		60 (23.2)	49 (18.9)	
T stage			0.276			0.688
T1+T2	68 (25.7)	119 (22.2)		65 (25.2)	69 (26.7)	
T3+T4	197 (74.3)	417 (77.8)		193 (74.8)	189 (73.3)	
N stage			0.862			0.697
N0+N1	79 (29.8)	163 (30.4)		76(29.5)	72 (27.9)	
N2+N3	186 (70.2)	373 (69.6)		182 (70.5)	186 (72.1)	
Clinical stage			0.175			0.405
III	180 (67.9)	338 (63.1)		173 (67.1)	164 (63.6)	
IV	85 (32.1)	198 (36.9)		85 (32.9)	94 (36.4)	
Smoking			0.013			0.465
Yes	91 (34.3)	233 (43.5)		91 (35.3)	99 (38.4)	
No	174 (65.7)	303 (56.5)		167 (64.7)	159 (61.6)	
Cisplatin dose of CCRT (mg/mš)			0.001			0.924
<200	186 (70.2)	298 (55.6)		179 (69.4)	180 (69.8)	
≥200	79 (29.8)	238 (44.4)		79 (30.6)	78 (30.2)	
Cisplatin dose of IC (mg/mš)			0.003			0.791
<150	143 (54.0)	229 (42.7)		136 (52.7)	133 (51.6)	
≥150	122 (46.0)	307 (57.3)		122 (47.3)	125 (48.4)	
Docetaxel dose of IC (mg/mš)			0.169			0.929
<150	156 (58.9)	288 (53.7)		149 (57.8)	148 (57.4)	
≥150	109 (41.1)	248 (46.3)		109 (42.2)	110 (42.6)	
Histology			0.917			0.788
I	1 (0.4)	1 (0.2)		1 (0.4)	0 (0)	
II	6 (2.2)	14 (2.6)		6 (2.3)	8 (3.1)	
III	258 (97.4)	521 (97.2)		251 (97.2)	250 (96.9)	

Note. IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; TPF, docetaxel, cisplatin and fluorouracil; TP, docetaxel and cisplatin.

3.1 | Survival results before propensity score matching

The median follow-up time was 60 months (range: 5–124 months). The 5-year OS, PFS, DMFS and LRRFS of 801 patients were 84.2%, 79.6%, 84.7% and 91.7%, respectively. The 5-year OS (85.8% *vs* 81.9%; $P = 0.037$; Figure 2a), PFS (84.6% *vs* 76.8%; $P = 0.008$; Figure 2b) and DMFS (89.5% *vs* 82.3%; $P = 0.004$, Figure 2c) were lower in the TP group than in the TPF group. There were no significant differences in the 5-year LRRFS (93.2% *vs* 91.0%, $P = 0.332$, Figure 2d) between the two groups.

3.2 | Survival results after PSM

After PSM, the TPF and TP groups each had 258 patients. The median follow-up time was 63 months (range: 5–124 months). The survival analysis results showed no significant differences in the 5-year LRRFS (91.9% *vs* 90.7%, $P = 0.436$; Figure 3d) between the TPF and TP groups. The 5-year OS, PFS and DMFS were higher in the TPF group than in the TP group (85.5% *vs* 80.8%, respectively, $P = 0.048$; Figure 3a; 84.2% *vs* 75.0%, respectively, $P = 0.009$, Figure 3b; and 89.2% *vs* 81.4%, respectively, $P = 0.006$, Figure 3c).

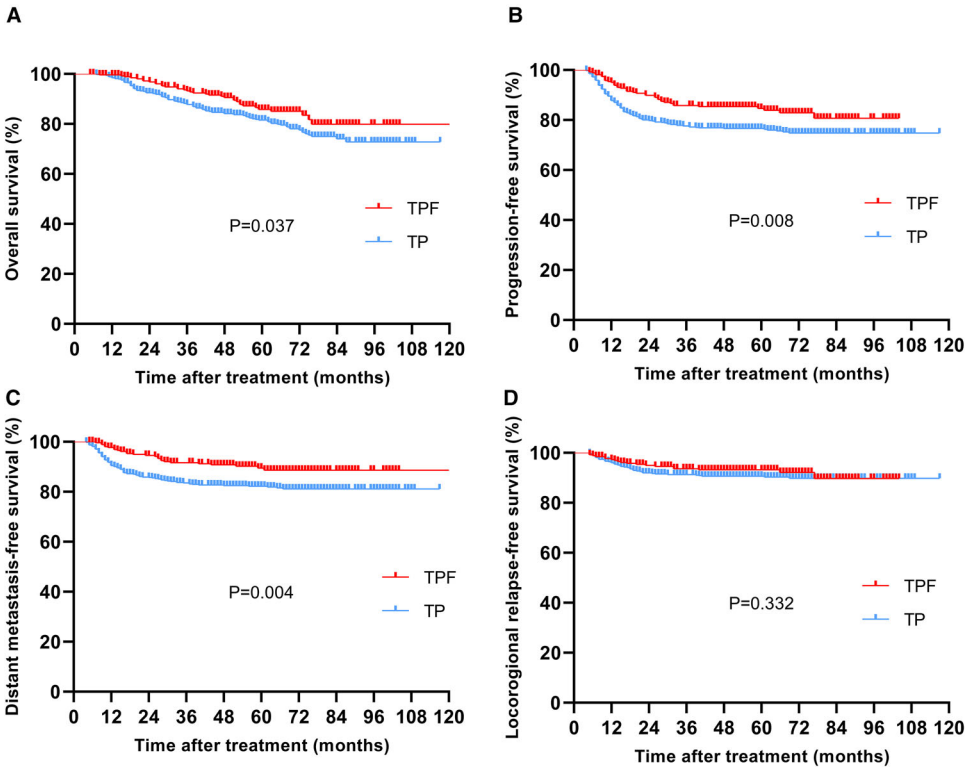

FIGURE 2 Kaplan–Meier survival curves based on the IC regimens of docetaxel and cisplatin (TP) versus docetaxel, cisplatin and fluorouracil (TPF) for the entire cohort. (a) Overall survival; (b) progression-free survival; (c) distant metastasis-free survival and (d) locoregional relapse-free survival [Colour figure can be viewed at wileyonlinelibrary.com]

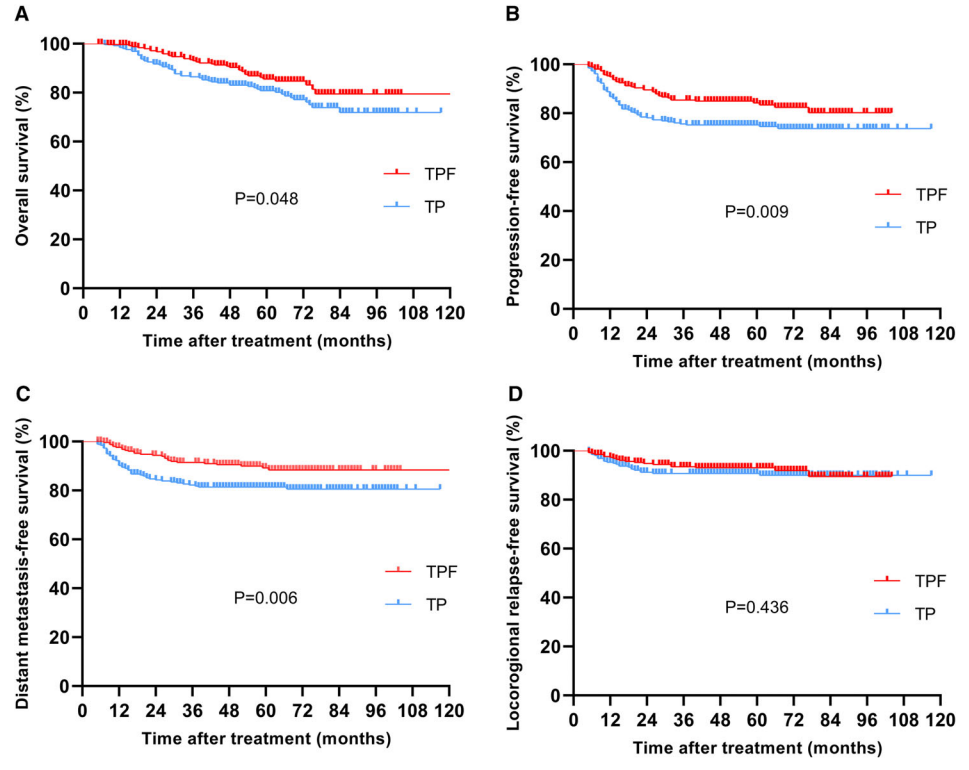

FIGURE 3 Kaplan–Meier survival curves based on the IC regimens of docetaxel and cisplatin (TP) versus docetaxel, cisplatin and fluorouracil (TPF) for the propensity-matched cohort. (a) Overall survival; (b) progression-free survival; (c) distant metastasis-free survival and (d) Locoregional relapse-free survival [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariate analyses of prognostic factors in 516 patients with nasopharyngeal carcinoma after PSM

	OS		PFS		DMFS		LRFS	
Variable	HR(95% CI)	*P*	HR(95% CI)	*P*	HR(95% CI)	*P*	HR(95% CI)	*P*
IC regimen(TP *vs* TPF)	0.684 (0.447–1.047)	0.081	0.610 (0.412–0.903)	0.014	0.532 (0.330–0.859)	0.010	0.792 (0.432–1.451)	0.450
Gender (male *vs* female)	0.675 (0.368–1.237)	0.203	0.579 (0.325–1.030)	0.063	0.445 (0.218–0.908)	0.026	0.973 (0.428–2.216)	0.949
Age (≤47 *vs* > 47)	1.627 (1.051–2.516)	0.029	1.340 (0.900–1.995)	0.149	1.425 (0.884–2.300)	0.146	1.533 (0.824–2.853)	0.177
Smoking (yes *vs* no)	0.934 (0.587–1.487)	0.774	0.977 (0.639–1.494)	0.913	0.731 (0.438–1.219)	0.229	0.770 (0.519–1.143)	0.715
T stage (T1+T2 *vs*T3+T4)	0.742 (0.448–1.229)	0.247	0.946 (0.593–1.512)	0.818	0.804 (0.469–1.378)	0.427	1.421 (0.621–3.255)	0.405
N stage (N0+N1 *vs* N2+N3)	1.647 (0.942–2.880)	0.080	2.325 (1.344–4.022)	0.003	2.753 (1.364–5.555)	0.005	1.706 (0.786–3.701)	0.176
Clinical stage (III *vs* IV)	2.327 (1.494–3.626)	0.000	2.217 (1.474–3.335)	0.000	2.150 (1.321–3.500)	0.002	2.892 (1.516–5.514)	0.001
cisplatin dose of CCRT (<200 *vs* ≥200 mg/mš)	1.185 (0.762–1.842)	0.452	0.802 (0.518–1.240)	0.320	0.952 (0.575–1.575)	0.848	0.825 (0.541–1.260)	0.374
cisplatin dose of IC (< 150 *vs* ≥150 mg/mš)	0.463 (0.231–0.924)	0.029	0.535 (0.286–1.000)	0.050	0.487 (0.230–1.031)	0.060	0.543 (0.195–1.513)	0.243
docetaxel dose of IC (< 150 *vs* ≥150 mg/mš)	0.472 (0.239–0.932)	0.031	0.590 (0.318–1.093)	0.093	0.571 (0.273–1.193)	0.136	0.637 (0.231–1.754)	0.382

Note. IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; TPF, docetaxel, cisplatin and fluorouracil; TP, docetaxel and cisplatin.

TABLE 3 Comparison of the side effects of the two groups after propensity score matching

	TP regimen (case%)		TPF regimen (case%)		
Adverse event	Grade 0–2	Grade 3–4	Grade 0–2	Grade 3–4	*P*-value
Leukocytopenia	149 (57.8)	109 (42.2)	160 (62.0)	98 (38.0)	0.323
Neutropenia	176 (68.2)	82 (31.8)	177 (68.6)	81 (31.4)	0.925
Anemia	244 (94.6)	14 (5.4)	239 (92.6)	19 (7.4)	0.368
Thrombocytopenia	250 (96.9)	8 (3.1)	248 (96.1)	10 (3.9)	0.631
Liver function	253 (98.1)	5 (1.9)	251 (97.3)	7 (2.7)	0.772
Renal function	255 (98.8)	3 (1.2)	254 (98.4)	4 (1.6)	1.000
Oral mucositis	193 (74.8)	65 (25.2)	145 (56.2)	113 (43.8)	0.001
Nausea/vomiting	235 (91.1)	23 (8.9)	184 (71.3)	74 (28.7)	0.001

Note. TPF, docetaxel, cisplatin and fluorouracil; TP, docetaxel and cisplatin.

The multivariate analysis showed that compared with the TP regimen, IC with TPF could significantly improve PFS (HR = 0.610; 95% CI, 0.412–0.903; $P = 0.014$) and DMFS (HR = 0.532; 95% CI, 0.330–0.859; $P = 0.010$). Clinical staging was an independent prognostic factor for OS, PFS, DMFS and LRRFS (Table 2).

3.3 | Toxicity

The adverse events of the TPF and TP groups were compared by the chi-squared test or Fisher's exact test in the PSM cohort. The incidence of oromucosal and nausea/vomiting reactions in the TPF group was higher than that in the TP group (all $P < 0.05$). Grade 3/4 hematotoxicity showed no significant difference in the two groups (all $P > 0.05$), mainly represented as leukopenia and neutropenia. Grade 3/4 anemia and decreased hemoglobin as well as grade 3/4 hepatic and renal function impairment only occurred in a small number of patients (Table 3).

4 | DISCUSSION

This retrospective nonrandomized study investigated the efficacy of different IC regimens on the prognosis of patients with locoregionally advanced NPC in the era of IMRT. The results showed that TPF induction chemotherapy increased OS, PFS and DMFS compared with TP induction chemotherapy and that the side effects of the TPF regimen were also clinically controllable. To control for potential confounding factors, PSM analysis was also performed in this study; the conclusion was consistent with that before PSM analysis, suggesting the reliability of the findings in a certain sense.

At present, as most patients with NPC are diagnosed at the intermediate and advanced stages, it is difficult to achieve good outcomes with CCRT alone. IC can reduce distant metastasis, eliminate microscopic lesions, reduce the proportion of hypoxic cells and improve sensitivity to radiotherapy.[13,14] An early IC trial, Tax323/324, demonstrated for the first time the clinical value of the IC regimen in head and neck tumors.[15,16] Subsequently, a phase III prospective randomized clinical study comparing IC+CCRT followed by CCRT in patients with locoregionally advanced NPC showed improved 3-year failure-free survival (FFS; 80% *vs* 72%, $P = 0.034$), demonstrating that IC could improve the prognosis of patients with locoregionally advanced NPC.[8] In recent years, several large clinical studies have demonstrated the clinical value of IC in the treatment of NPC.[7,17] Although much evidence has shown that IC can improve the prognosis in patients with locoregionally advanced NPC, the optimal treatment from numerous IC regimens is still uncertain.

The TP regimen is one of three IC regimens recommended by the NCCN Guidelines.[9] Taxanes show great monotherapy activity and radiotherapy sensitization in head and neck cancer. Moreover, previous studies have also shown that cisplatin combined with taxanes can enhance the therapeutic efficacy and effectively prevent patients with head and neck squamous cell carcinoma from developing drug resistance.[18–20] Yeo et al.[21] found that the TP regimen was effective for locoregionally advanced NPC with a total remission rate of 59%, of which complete remission (CR) accounted for 11% and partial remission (PR) 48%. A prospective study in 2009 showed that compared with CCRT alone, TP+CCRT significantly improved the 3-year OS in patients with locoregionally advanced NPC (94.1% *vs* 67.7%, $P = 0.012$).[11] These findings demonstrated the clinical value of the TP regimen in locoregionally advanced NPC.

Fluorouracil kills tumor cells by inhibiting thymidine synthase (TS), thereby affecting DNA synthesis.[22] Fluorouracil combined with radiotherapy can also produce a synergistic effect of radiotherapy sensitization.[23] It has a therapeutic effect on NPC as well as on head and neck tumors in other sites.[24,25] Nevertheless, whether continued addition of fluorouracil to TP can further improve the prognosis of patients should be further investigated.

The NCCN Guidelines recommended three IC regimens for NPC, that is, TPF, TP and cisplatin plus fluorouracil (PF) regimens.[9] Recently, studies comparing two- and three-drug therapies have arisen because fewer drugs will produce fewer side effects. One retrospective study showed that the 5-year OS, DSS and DMFS in the TPF group were 88.1%, 88.5% and 87.9%, respectively, higher than the rates of 80.7%, 80.7% and 78.6% in the PF group ($P = 0.042$, 0.021 and 0.013, respectively). This study led to the decline of the PF regimen as a result. However, we also noted that although adverse reaction events were clinically controllable, the incidence and extent of adverse events in the TPF group were significantly higher than those in the PF group.[10] Whether the TP regimen is a good trade-off compared to that of the TPF regimen still needs to be further explored.

This retrospective nonrandomized study demonstrated for the first time that the TPF induction chemotherapy regimen was more effective than a TP regimen on locoregionally advanced NPC patients by long-term follow-up visits of a large-sample population. Noronha et al.[26] found in a prospective study in 26 patients with locoregionally advanced head and neck squamous cell carcinoma that TP was a feasible IC regimen with equivalent efficacy to TPF by comparing the outcomes of TP and TPF. We also noted that because NPC has different epidemiology, histology, clinical behavior and treatment response from other head and neck cancers, whether the results of Noronha et al[26] are applicable in NPC patients should be further demonstrated; moreover, the results of their study were only somewhat persuasive due to the study's small sample size and short median follow-up time.

In terms of toxicity, the two regimens used in this study demonstrated good overall tolerance, but the incidence of grade 3/4 nausea/vomiting and oromucosal toxicity was higher in the TPF group than in the TP group (all $P < 0.05$); this was consistent with recent findings, suggesting that TPF can produce more severe gastrointestinal and mucosal toxicity than TP[27]. We believe that the addition of fluorouracil may be responsible for nausea/vomiting and oromucosal toxicity. However, TP and TPF may produce similar hematotoxicity. Grade 3/4 hematotoxicity were represented as leukopenia and neutropenia, which occurred in 40.1% and 31.6% of the total population in the two groups, respectively, whereas the use of granulocyte colony-stimulating factor (G-CSF) may be responsible for the same incidence of leukopenia and neutropenia in both groups. Meanwhile, grade 3/4 anemia and thrombocytopenia were easy to manage due to their low incidence. Neither group of patients had serious liver function injury or acute renal function impairment, and only one patient in the TPF group suffered grade 3/4 renal function impairment.

This retrospective analysis used PSM to exclude confounding factors by matching accurately rather than fuzzily, which can eliminate the impacts of other potential confounding variables. Nevertheless, this retrospective study has some deficiencies because it cannot eliminate interference from some potential factors and has limited accuracy, as the data of oromucosal and nausea/vomiting toxic reactions are derived from daily case records instead of prospective records. At the same time, since EBV-DNA testing was not widely available in previous years, the lack of EBV-DNA is a limitation of this work.

5 | CONCLUSION

This study found that compared with the TP regimen, TPF induction chemotherapy combined with CCRT can improve the survival of patients with locoregionally advanced NPC, mainly in terms of PFS and DMFS, and TPF can produce more mucosal and nausea/vomiting adverse reactions than TP. Given the limitations of retrospective data, relevant findings should be confirmed through prospective clinical studies with a large sample size.

AUTHORS' CONTRIBUTIONS

Rong-Hui Zheng and Tai-Ze Yuan were guarantors of the entire study. Rong-Hui Zheng, Tai-Ze Yuan, Ze-Jiang Zhan and Hao-Yun Tao built up the study concepts and designed this study. Hao-Yun Tao, Wen-Ze Qiu and Kai Liao collected clinical data all needed. Wen-Ze Qiu and Ya-Wei

Yuan performed the statistical analyses. Rong-Hui Zheng, Tai-Ze Yuan, Ze-Jiang Zhan and Hao-Yun Tao prepared and edited the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

No conflicts of interest exists.

ETHICAL APPROVAL

This study has been approved by the ethics committee of our hospital, and it has therefore been performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki and its subsequent amendments.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available in the Figshare repository https://figshare.com/s/716ad8287a82ac218848.

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