Comparison of TPF and TP Induction Chemotherapy for Locally Advanced Nasopharyngeal Carcinoma Based on TNM Stage and Pretreatment Systemic Immune-Inflammation Index

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Abstract

Background: Induction chemotherapy (IC) was associated with a decreased risk of distant metastasis in locally advanced nasopharyngeal carcinoma (LA-NPC). However, compared with TPF, whether the TP regimen can reduce the related toxicities caused by 5-FU while ensuring the survival benefit remains unclear.

Methods: 213 patients diagnosed with LA-NPC (stage III-IVA) were included retrospectively. The prognosis of TPF and TP was compared by Kaplan-Meier and Cox proportional hazard regression. The treatment-related toxicities were evaluated according to CTCAE v4.0 and RTOG criteria.

Results: TPF was found to have a higher 5-year DMFS in stage IVA and N2-3 patients, which not applicable to stage III and N0-1. The optimal value of pre-treatment SII was 432.48. A further subgroup analysis revealed that patients in stage IVA combined with pretreatment SII≥432.48 could get higher OS (*P*=0.038) and DMFS (*P*=0.028) from TPF. Multivariate analysis showed that SII was a prognostic factor for PFS (HR 2.801, *P*=0.018) and DMFS (HR 3.735, *P*=0.032), and IC regimen (HR 2.182, *P*=0.049) for predicting DMFS. The rate of grade 3-4 leukopenia (*P*=0.038), neutropenia (*P*=0.021), radiation oral mucositis (*P*=0.048) and diarrhea (*P*=0.036) were more common in TPF group.

Conclusion: Our study revealed that TPF regimen showed a higher 5-year DMFS for stage IVA and N2-3 patients, while TP may be enough for stage III and N0-1. In LA-NPC patients with high risk (stage IVA combined with pre-treatment SII ≥ 432.48), TPF had a higher 5-year OS and DMFS, although grade 3-4 toxicities were more common but tolerable.

Introduction

Nasopharyngeal carcinoma (NPC), a malignant tumor derived from epithelial cells of the nasopharynxin of the head and neck region in China and Southeast Asia, with 129,000 new cases diagnosed worldwide [1]. Early symptoms are hidden and 75% patients have been diagnosed with NPC at stage III or IVA. Due to its special anatomy and sensitivity to radiation, concurrent chemoradiotherapy (CCRT) is the main treatment modality for locally advanced NPC (LA-NPC). With the application of intensity-modulated radiotherapy (IMRT), local control rates of LA-NPC were improved, however, distant metastasis still remains a major failure pattern.

Increased clinical evidence supports induction chemotherapy (IC) can contribute to control subclinical micrometastasis [2]. A phase III trial [3] showed that compared with CCRT, IC combined with CCRT could improve overall survival (OS), disease-free survival (DFS) and distant metastasis-free survival (DMFS) in LA-NPC. A recent study [4] showed that IC plus CCRT could increase OS ($P < 0.001$), PFS ($P < 0.001$), DMFS ($P < 0.001$) and LRFS ($P < 0.001$) in LA-NPC. Similarly, the survival benefits brought by IC followed by CCRT have been confirmed in many other studies [5]. As a result, IC followed by CCRT is suggested in the category 1A recommendations for LA-NPC according to the National Comprehensive Cancer Network (NCCN) guidelines [6].

The first-line IC regimens including Docetaxel, cisplatin, and 5-fluorouracil (TPF), Docetaxel and cisplatin (TP), Gemcitabine and cisplatin (GP) have shown some survival advantages in studies [7]. At present, TPF is the main regimen, but accompanied by its long treatment time and adverse reactions caused by 5-FU, such as myelosuppression and diarrhea. Therefore, it is crucial whether the TP regimen can reduce the related toxicities while ensuring the survival benefit. A phase II clinical trial conducted by Wang et al.[8] in LA-NPC showed that, TPF (docetaxel 60mg/m^2, cisplatin 25mg/m^2, day 1–3, 5-FU 500mg/m^2, day 1–3) had similar efficacy compared to TP, and the grade 3–4 toxicity in TP group is lower, which provided an idea for TP regimen as an alternative to TPF. However, the standard dose of 5-FU was lowered as considering the tolerance of patients, so we could not completely rule out the potential effect of dose. At present, there is still no consensus about the efficacy and safety of the two regimens. Therefore, this paper was conducted to compare the efficacy and toxicity of TPF and TP regimen in LA-NPC patients, in order to explore the feasibility of alternative TP regimen.

In addition, the TNM staging system is still used as the gold standard for predicting the prognosis of NPC, but the prognosis of patients who received similar treatment in the same period is different, as the internal tumor heterogeneity is not taken into account by TNM staging. Nowadays, accumulating evidence have shown that inflammation can promote the development, growth and metastasis of tumor cells [9]. And systemic immune-inflammation index (SII), a new hematological index, has been identified as a prognostic biomarker in NPC [10]. It is worth pointing out that, patients with NPC in our analysis were divided into different subgroups according to the pretreatment SII levels, which was not reported in previous studies.

Patients And Methods

Patients

213 patients diagnosed with LA-NPC at Union Hospital Cancer Center from January 2013 and December 2017 were enrolled. The inclusion criteria were as follows: 1) 16 ≤ age ≤ 70 years, 2) histologically confirmed NPC, 3) Karnofsky performance score (KPS) ≥70, 4) detailed medical records, including nasopharyngeal speculum, contrast-enhanced MRI of the nasopharynx and neck, chest CT, abdominal ultrasonography and whole-body bone scan or PET-CT for stage, re-staged III-IVA based on the 8th edition of the AJCC staging system, 5) completion of IC followed by CCRT, and 6) complete data of hematological parameters, including neutrophil, lymphocyte and platelet counts within 1 week before therapy. The exclusion criteria were as follows: 1) evidence of concomitant tumors at diagnosis, 2) a history of anticancer therapy, 3) insufficient heart, lung, liver and renal function, and 4) severe anemia, acute infection or autoimmune diseases. Written consent was obtained from all enrolled patients and the study was approved by Cancer center of Union hospital of Tongji medical college of Huazhong university of science and technology.

Methods

According to our institution guidelines, the total prescribed IMRT dose was 66-76Gy/33F to the gross tumor volume of the nasopharynx (GTVnx), 66-70Gy/33F to the gross tumor volume of the positive neck

lymph nodes (GTVnd), 60-66Gy/33F to the clinical target volume 1 (CTV1), and 54-60Gy/33F to the clinical target volume 2 (CTV2). PTVs were delineated by adding 5 mm and 3 mm to the GTV and CTV, respectively. The fractionated dose was 1.8 to 2.2 Gy at 1 fraction per day on 5 days per week. The regimens of IC were as follows: 1) TPF regimen: docetaxel (75 mg/m^2/day, day 1), cisplatin (75 mg/m^2/day, day 1), and 5-fluorouracil (750 mg/m^2/day, day 1-5), and 2) TP regimen: docetaxel (75 mg/m^2/day, day 1) and cisplatin (75 mg/m^2/day, day 1). IC were prescribed every 3 weeks for three cycles. Moreover, concurrent chemotherapy consisted of cisplatin sensitization with a total dose of 200 mg/m^2.

Data collection and clinical endpoints

All peripheral blood samples were collected from EDTA anticoagulant tube and measured for neutrophil, lymphocyte and total platelet count within 1 week before treatment. The definition of the SII is described as follows: SII = total platelet count (10^9/L) ×total neutrophil count (10^9/L) / total lymphocyte count (10^9/L). The end points were: Overall survival (OS), which was defined as the time between pathological diagnosis and the death of any cause or the last follow-up. Progression-free survival (PFS), defined as the time that had elapsed between pathological diagnosis and the date of disease progression or death from any cause. Locoregional relapse-free survival (LRFS) was defined as the time from pathological diagnosis to local relapse. Distant metastasis-free survival (DMFS) was defined as the time from pathological diagnosis to the time of distant metastasis detection.

Treatment-related side effects between the groups were evaluated according to CTCAE V4.0 (Common Terminology Criteria for Adverse Events V4.0) [11] and RTOG (Radiation Therapy Oncology Group) criteria [12].

Follow-up

All patients were evaluated every 3 months for the first 2 years after complete treatment, every 6 months between the third to fifth year, then evaluated annually. A nasopharyngeal speculum, contrast-enhanced MRI of the nasopharynx and neck, chest CT, abdominal ultrasonography, and a whole-body bone scan was examined. The last follow-up took place on January 2020. All patients went followed up by each clinical examination in the hospital or telephone calls.

Statistical analyses

The cutoff value of SII was determined by receiver operating characteristic (ROC) curve. Chi-square test was used to investigate difference between the SII subgroups. Survival curves were analyzed by the Kaplan-Meier method, and univariate analysis by the log-rank method. Cox proportional hazards regression model was used for multivariate analysis. Statistical analysis was conducted using SPSS 25.0 and GraphPad Prism 8.0. A two-tailed *P* value less than 0.05 was considered statistically significant.

Results

Baseline characteristics and follow-up

Ultimately, a total of 213 LA-NPC patients were included in the study, with 128 and 85 patients in the TPF and TP group, respectively. The baseline characteristics of these two groups are shown in Table 1. Among them, 155 (72.77%) were males and 58 (27.23%) were females, with ages ranging from 22 to 69 years (median 45 years). 101 (47.42%) and 87 (40.85%) patients with a history of smoking and drinking. In the cohort, 121 (56.81%) patients were diagnosed with positive EBV DNA status. Based on the TNM staging system, 115 (53.99%) and 98(46.01%) patients were re-staged in stage III and IVA, respectively. The cut off value of SII was 432.48 according to the ROC curve (Fig. 1). And patients were divided into low and high SII groups, with 67 (31.46%) and 146 (68.64%) cases, respectively.

As shown in the table, no significant difference was found in the two regimen groups ($P > 0.05$). The latest follow-up was finished at the end of January 2020. In total, the median follow-up time was 44 (26-83) months. Finally, 20 (9.39%) patients died and 54 (25.35%) patients suffered from tumor progression. The 5-year OS, PFS, LRFS and DMFS rates in TPF and TP groups were 89.0% vs 82.4%, 76.8% vs 68.4%, 85.9% vs 86.9% and 90.2% vs 81.3%, respectively.

Survival analysis based on TNM staging system

Survival curves based on the different IC regimens were analyzed using the Kaplan-Meier method. As was shown in Fig. 2, compared with the TP group, the patients in TPF group had a higher 5-year DMFS rate (90.2% vs 81.3%, $P = 0.043$, Fig. 2D). However, there was no significant difference in OS, PFS and LRFS between the two groups ($P > 0.050$).

Patients in different TNM stage showed different tumor load and treatment failure rate. Therefore, survival differences among patients in different clinical and N stage subgroups were conducted separately, with 98 in stage III and 115 in stage IVA. Since only 5 stage N0 patients were included, in order to minimize the deviation of statistical analysis, we divided N stage into N0-1 and N2-3 subgroups, including 50 and 163 cases respectively. According shown in Fig. 3, there was an evident survival difference between the two groups in patients with stage IVA, the TPF group had superior PFS ($P = 0.042$, Fig. 3B) and DMFS ($P = 0.033$, Fig. 3D). Similarly, we found that stage N2-3 patients in TPF also showed a significant trend in a higher DMFS ($P = 0.057$, Supplementary Fig. 3). However, in patients with stage III and N0-1, no survival difference was found ($P > 0.050$, Supplementary Fig. 3).

Survival analysis in stage IVA patients combined with pretreatment SII

Moreover, SII is a promising factor in predicting prognosis of NPC patients. Therefore, patients in stage IVA were divided into low and high-risk subgroups according to different SII levels. Interestingly, our results revealed that in the high-risk group (SII≥432.48), TPF showed significantly better OS ($P = 0.038$, Fig. 4A) and DMFS ($P = 0.028$, Fig. 4D) than TP. Further analysis was conducted and demonstrated that there was no significant difference between IC regimens and survival prognosis in the low-risk group (SII < 432.48), however, there were only 16 and 10 cases in TPF and TP groups, respectively, which required larger samples to confirm.

Univariate and Multivariate analysis

In our univariate analysis, EBV DNA status, TNM stage and pretreatment SII were corroborated as potential factors affecting all survival outcomes (Table 2). The 5-year DMFS rate of patients with N0-1 stage is higher than that of N2-3 (88.3% vs 84.6%, $P = 0.038$). And in different IC regimens, the 5-year DMFS rate in the TPF group was higher (90.2% vs 81.3%, $P = 0.043$). Considering the confounding factors, variables that reached a significant difference in the univariate analysis were further analyzed in multivariate Cox regression analysis. As shown in Table 3, EBV DNA status and clinical stage were related factors affecting OS, PFS, LRFS and DMFS ($P < 0.050$). The pretreatment SII level was an independent prognostic factor for PFS (HR 2.801, 95% CI 1.195-6.565, $P = 0.018$) and DMFS (HR 3.735, 95% CI 1.121-12.441, $P = 0.032$). At the same time, IC regimen (HR 2.182, 95% CI 1.002-4.751, $P = 0.049$) and N stage (HR 4.076, 95% CI 0.962-7.267, $P = 0.046$) can also be used as effective indicators for predicting DMFS in LA-NPC patients.

Toxicities

As shown in Table 4, there was no significant difference in grade 1-2 toxicities between the two groups ($P > 0.050$). Compared with TP regimen, we found that the rate of grade 3-4 leukopenia (40.62% vs 36.47%, $P = 0.038$), neutropenia (27.34% vs 14.12%, $P = 0.021$), radiation oral mucositis (28.91% vs 14.12%, $P = 0.048$) and diarrhea (27.34% vs 10.59%, $P = 0.036$) was higher in the TPF group. All the patients with toxicities were improved after treatment, and no interruption of treatment occurred.

Discussion

Distant metastasis still remains a crucial problem in the treatment of LA-NPC patients. With the improvement of IMRT, the local control rate has improved; however, distant metastasis remains a major cause of treatment failure [13]. Increasing evidences suggested that IC can promote the eradication of micro metastasis, alleviate clinical symptoms caused in short term and improve radiosensitivity [14]. Furthermore, IC has been confirmed to be effective with LA-NPC in several phase III trials[15] and is widely applied. Therefore, the use of IC followed by CCRT is recommended to improve survival benefit in LA-NPC. However, it is quite important to find effective IC regimens with fewer side effects. Currently, studies on IC regimens commonly used in LA-NPC include TPF, TP, PF and GP [16]. Zhao et al. [17] found that compared with PF regimen, both GP and TP regimens could significantly improve DFS and OS, and no severe toxicities occurred. And Peng et al. [18] concluded that induction TP regimen may be enough for patients receiving a cumulative cisplatin dose (CCD) $\geq$ 200 mg/m^2, while TPF may be superior to TP and PF for patients receiving a CCD < 200 mg/m^2.

At present, TPF is the main regimen for LA-NPC, but accompanied by its long treatment time and adverse toxicities caused by 5-FU, such as myelosuppression and diarrhea. In a previous study on locally advanced head and neck squamous cell carcinoma [19], it was found that the total effective rate of TP regimen was 65.4%. The 3-year PFS rate and OS rate was similar as TPF. What is known to us all, different tumors of the head and neck were included in that study, and the response rate of TP regimen was taken as the main end point. Wang et al. [8] further found that TPF (docetaxel 60mg/m2, cisplatin 25mg/m2, day 1–3, 5-FU

500mg/m2, day 1–3) showed similar efficacy compared to TP. There was no significant difference in 3-year OS, PFS, LRFS, DMFS rate ($P > 0.050$) between the two regimens. And multivariate analysis in this study also showed that IC regimen was not an independent prognostic factor for survival, however, the grade 3–4 toxicity in TP group is lower and tolerable. On accounting of the toxicities of 5-FU, patients were given lower dosage, so the potential effect of insufficient dose cannot be completely ruled out. At present, there is still no consensus about the efficacy and safety of the two regimens. Therefore, this paper was conducted to compare the efficacy and toxicity of TPF and TP regimen in LA-NPC, in order to explore the feasibility of alternative TP regimen.

Finally, 213 LA-NPC patients were enrolled in our study. It was found that there was no significant difference in the short-term efficacy between the two groups (total effective rate was 79.7% vs 78.8%), and no significance in 5-year OS, PFS and LRFS ($P > 0.050$), which were consistent with Peng [18] and Wang et al. [8] Variously, in our study, TPF was found to have a higher 5-year DMFS rate (90.2% vs 81.3% 750mg/m^2, $P = 0.043$), which may be due to the therapeutic benefits of 5-FU. Compared with the study of Wang et al. [8] (5-FU 500mg/m^2, days 1–3), the dose in our hospital reached 750mg/m^2 (days 1–5) in TPF regimen. Similarly, in the NPC-9901 and NPC-9902 study [20], the dose of 5-FU during CCRT was confirmed to improve DFFS, with an explanation that 5-FU could reduce the risk of disease and this may also be applicable to the IC phase. At present, TNM stage is still the gold standard for predicting prognosis, and we further analyzed survival differences between patients in stage III and IVA, respectively. Interestingly, the same results were found in stage IVA patients. Advanced N category (N2-3) is well recognized as a risk factor for distant metastasis [21], in our N category subgroups, fortunately, we observed that the TPF group had a trend in higher 5-year DMFS ($P = 0.057$), which was not applicable in N0-1. One possible explanation is that TPF can reduce distant metastases from patients with high metastatic burdens (N2-3). Similarly, Guo et al. [22] found that N3 is an independent prognostic factor for LA-NPC, with poorer survival. These findings are similar to the results of our study, that is, compared with TP regimen, TPF regimen can show better survival in LA-NPC, especially in N2-3 patients. For N0-1 patients, the choice of TP regimen with fewer treatment-related toxicities may be enough.

In recent years, more and more evidences supported systemic inflammation plays an important role in tumor development and metastasis [23]. SII is associated with poor prognosis of NPC as a new biomarker [10], which defined as a combination of neutrophil, platelet and lymphocyte count. It is a comprehensive and objective tool that integrates three indicators together, and it is simpler and cheaper. Oei et al. [24] revealed SII was an independent prognostic factor for OS, PFS, and DMFS ($P < 0.05$). In our study, it was also confirmed that pretreatment SII was an independent prognostic factor of PFS (HR 2.801, $P = 0.018$) and DMFS (HR 3.735, $P = 0.032$), which was consistent with the previous results. However, the cut off values of SII were inconsistent in studies, which may be due to the basic level of the enrolled patients with different stages and the difference of sensitivity and reference value of reagent instrument. On the other hand, as a retrospective study with a relatively small sample size obtained at a single center, although SII is an independent predictor of NPC prognosis, its sensitivity, and specificity are not necessarily very high, indicating that further prospective studies are required to determine the appropriate cutoff value.

The prognostic effect of SII may be explained by its composition. In inflammatory cells, neutrophils can secrete inflammatory mediators, such as IL-6 and TNF, to promote cancer cell invasion, proliferation, and metastasis [25]. Lymphocytes can regulate tumor growth by secreting cytokines such as IFN-γ and TNF-α to regulate tumor growth. Platelet can increase the number of circulating tumor cells (CTCs) and promote extravasation of tumor cells into metastatic sites [26]. Therefore, the combination of high neutrophil count, high platelet count and low lymphocyte count, defined as a high SII, can promote tumor cell proliferation and metastasis to poor prognosis. To our knowledge, this is the first study to report the prognostic value of IC regimens based on pretreatment SII and TNM stage in LA-NPC. According to ROC curve, the patients in stage IVA with SII ≥ 432.48 was defined high-risk group. Interestingly, our results revealed that in the high-risk group, TPF was associated with significantly better OS (P = 0.038) and DMFS (P = 0.028) than TP, unfortunately, there was no significant difference in the low-risk group due to a small sample size. Hence, TPF could be considered as the more effective regimen, particularly in high-risk (IVA combined with SII ≥ 432.48) patients. Furthermore, multivariate analysis showed that IC regimen (HR 2.182, P = 0.049) and N stage (HR 4.076, P = 0.046) could also be used as effective indicators for predicting DMFS in LA-NPC patients.

About the treatment-related side effects, obviously, combinations of three drugs produce more grade 3–4 toxicities. In our study, we found that compared with TP, the rate of grade 3–4 leukopenia (P = 0.038), neutropenia (P = 0.021), radiation oral mucositis (P = 0.048) and diarrhea (P = 0.036) were more common in the TPF group, which was consistent as previously reported [8, 27]. This difference could be attributed to the anti-tumor therapy of 5-FU, since myelosuppression and diarrhea are the common toxicities.

However, our study also has some limitations. First, this study is a retrospective analysis with a small sample size, which may potentially bias our findings. And then, we only studied the pretreatment level of SII, dynamic levels of the indicators will be more meaningful. Therefore, further multicenter, large-sample, prospective randomized controlled trials are needed to validate these findings.

In summary, our study revealed that TPF regimen showed a higher 5-year DMFS for LA-NPC patients with stage IVA and N2-3, while TP may be enough for stage III and N0-1. In stage IVA combined with pre-treatment SII ≥ 432.48 patients, TPF had higher 5-year OS and DMFS, although grade 3–4 toxicities were more common but tolerable.

Declarations

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None.

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data availability

All data generated or analyzed during this study are available at xiongying0604@163.com.

Code availability

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Treatment and data collection were performed by Ying Xiong. Analysis was performed by Ying Xiong, Li sheng Zhu and Gang Peng. The first draft of the manuscript was written by Ying Xiong and Liang liang Shi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of Cancer center of Union hospital of Tongji medical college of Huazhong university of science and technology.

Consent for publication

For this type of study, formal consent is not required.

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Tables

Table 1 Baseline characteristics of patients in the TPF and TP groups.

Variables	TPF (n=128) (%)	TP (n=85) (%)	*P*
Age (years)			0.166
45	38 (29.69)	33 (38.82)	
≥45	90 (70.31)	52 (61.18)	
Sex			0.127
female	30 (23.44)	28 (32.94)	
male	98 (76.56)	57 (67.06)	
Smoke			
no	60 (46.88)	52 (61.18)	0.051
yes	68 (53.12)	33 (38.82)	
Drink			0.290
no	72 (56.25)	54 (63.53)	
yes	56 (43.75)	31 (36.47)	
EBV DNA status			0.628
negative	57(44.53)	35(41.18)	
positive	71(55.47)	50(58.82)	
Tumor classification			0.406
T1	1(0.78)	0(0.00)	
T2	18(14.06)	18(21.17)	
T3	56(43.75)	38(44.71)	
T4	53(41.41)	29(34.12)	
Nodal classification			0.213
N0	2(1.56)	3(3.53)	
N1	30(23.44)	15(17.65)	
N2	78(60.94)	47(55.29)	
N3	18(14.06)	20(23.53)	
Clinical stage			0.756
III	60(46.88)	38(44.71)	

IVA	68(53.12)	47(55.29)	
Pretreatment SII level			0.824
432.48	41 (32.03)	26 (30.59)	
≥432.48	87 (67.97)	59 (69.41)	

Abbreviations: TPF: docetaxel, cisplatin, and 5-fluorouracil, TP: docetaxel and cisplatin, EBV DNA: Epstein-Barr virus DNA, SII: systemic immune-inflammation index.

Table 2. Univariate analysis of prognostic factors for LA-NPC patients.

Variables	5-year OS（%）	*P*	5-year PFS（%）	*P*	5-year LRFS（%）	*P*	5-year DMFS（%）	*P*
Age (years)		0.494		0.636		0.537		0.298
45	88.0		72.0		88.7		83.2	
≥45	86.1		74.1		85.1		88.4	
Sex		0.800		0.688		0.392		0.624
female	84.9		70.8		81.0		89.7	
male	87.6		74.4		88.3		85.4	
Smoke		0.533		0.655		0.781		0.500
no	88.4		74.5		85.6		88.0	
yes	85.0		72.3		87.1		85.1	
Drink		0.798		0.599		0.700		0.164
no	86.2		74.7		85.6		89.1	
yes	87.1		71.4		87.2		83.0	
EBV DNA status		0.004		0.000		0.001		0.000
negative	96.0		93.3		95.5		97.8	
positive	80.8		59.0		79.4		78.5	
Tumor classification		0.393		0.259		0.333		0.535
T1-2	90.3		81.0		90.5		90.5	
T3-4	85.7		71.2		85.1		85.4	
Nodal classification		0.289		0.479		0.307		0.038
N0-1	91.6		68.1		78.8		88.3	
N2-3	85.7		73.3		88.0		84.6	
Clinical stage		0.000		0.001		0.001		0.000
III	99.0		99.0		99.0		99.0	
IVA	75.0		50.2		75.1		74.3	
Pretreatment SII level		0.002		0.000		0.008		0.021
432.48	100		91.0		95.5		95.5	

≥432.48	80.9		65.5		82.1		82.5	
IC regimen		0.154		0.080		0.924		0.043
TPF	89.0		76.8		85.9		90.2	
TP	82.4		68.4		86.9		81.3	

Abbreviations: EBV DNA: Epstein-Barr virus DNA, SII: systemic immune-inflammation index, IC: induction chemotherapy, TPF: docetaxel, cisplatin, and 5-fluorouracil, TP: docetaxel and cisplatin, OS: overall survival, PFS: progression-free survival, LRFS: locoregional relapse-free survival, DMFS: distant metastasis-free survival.

Table 3. Multivariate Cox regression analysis of prognostic factors for LA-NPC patients.

Variables	HR（95%CI）	*P*
OS		
EBV DNA status (positive vs negative)	6.456（1.496-7.871）	0.012
Nodal classification (N2-3 vs N0-1)	2.167（0.500-9.391）	0.301
Clinical stage (IVA vs III)	9.355（2.588-14.731）	0.004
Pretreatment SII level (≥432.48 vs < 432.48)	3.977（0.709-7.314）	0.073
IC regimen (TP vs TPF)	1.880（0.778-4.545）	0.161
PFS		
EBV DNA status (positive vs negative)	5.254（2.242-12.314）	0.001
Nodal classification (N2-3 vs N0-1)	0.887（0.637-1.236）	0.480
Clinical stage (IVA vs III)	4.956（5.898-12.845）	0.001
Pretreatment SII level (≥432.48 vs < 432.48)	2.801（1.195-6.565）	0.018
IC regimen (TP vs TPF)	1.604（0.941-2.736）	0.083
LRFS		
EBV DNA status (positive vs negative)	3.358（1.162-9.700）	0.025
Nodal classification (N2-3 vs N0-1)	0.665（0.303-1.463）	0.311
Clinical stage (IVA vs III)	1.479（2.477-7.839）	0.004
Pretreatment SII level (≥432.48 vs < 432.48)	0.665（0.303-1.463）	0.086
IC regimen (TP vs TPF)	1.036（0.495-2.172）	0.924
DMFS		
EBV DNA status (positive vs negative)	9.871（2.332-4.774）	0.002
Nodal classification (N2-3 vs N0-1)	4.076（0.962-7.267）	0.046
Clinical stage (IVA vs III)	5.201（2.769-5.011）	0.010
Pretreatment SII level (≥432.48 vs < 432.48)	3.735（1.121-12.441）	0.032
IC regimen (TP vs TPF)	2.182（1.002-4.751）	0.049

Abbreviations: EBV DNA: Epstein-Barr virus DNA, SII: systemic immune-inflammation index, IC: induction chemotherapy, TPF: docetaxel, cisplatin, and 5-fluorouracil, TP: docetaxel and cisplatin, OS: overall

survival, PFS: progression-free survival, LRFS: locoregional relapse-free survival, DMFS: distant metastasis-free survival, HR: hazard ratio, CI: confidence interval.

Table 4. Treatment-related toxicities between the TPF and TP groups.

Variables	TPF (n=128)			TP (n=85)			*P*	
	grade 0 (%)	grade 1-2 (%)	grade 3-4 (%)	grade 0 (%)	grade 1-2 (%)	grade 3-4 (%)	grade 1-2	grade 3-4
Leukopenia	20 (15.63)	56 (43.75)	52 (40.62)	24 (28.24)	30 (35.29)	31 (36.47)	0.380	0.038
Neutropenia	28 (21.88)	65 (50.78)	35 (27.34)	33 (38.82)	40 (47.06)	12 (14.12)	0.465	0.021
Anemia	46 (35.94)	78 (60.94)	4 (3.12)	36 (42.35)	47 (55.29)	2 (2.36)	0.583	0.154
Thrombocytopenia	44 (34.38)	82 (64.06)	2 (1.56)	28 (32.94)	56 (65.88)	1 (1.18)	0.435	0.083
Abnormal liver function	46 (35.94)	81 (63.28)	1 (0.78)	26 (30.59)	58 (68.23)	1 (1.18)	0.363	0.215
Abnormal renal function	48 (37.50)	79 (61.72)	1 (0.78)	32 (37.65)	53 (62.35)	0 (0.00)	0.672	0.276
Vomiting	23 (17.97)	90 (70.31)	15 (11.72)	12 (14.12)	59 (69.41)	14 (16.47)	0.574	0.426
Oral mucositis	26 (20.31)	65 (50.78)	37 (28.91)	23 (27.06)	50 (58.82)	12 (14.12)	0.375	0.048
Diarrhea	18 (14.06)	75 (58.60)	35 (27.34)	17 (20.00)	59 (69.41)	9 (10.59)	0.584	0.036

Abbreviations: TPF: docetaxel, cisplatin, and 5-fluorouracil, TP: docetaxel and cisplatin.

Figures

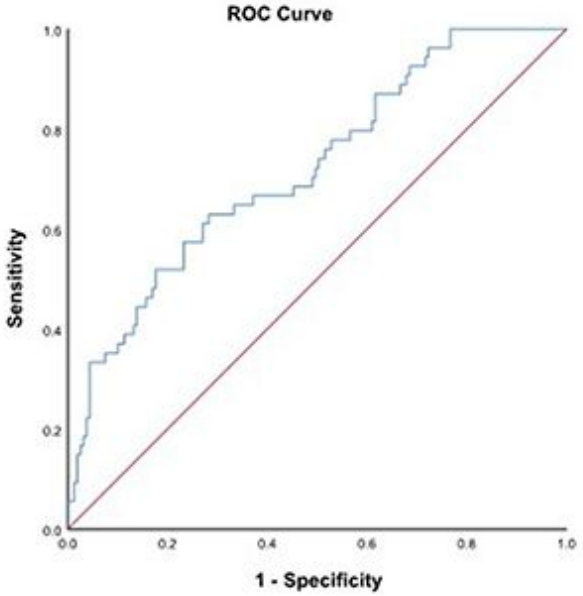

Figure 1

ROC curve for pretreatment SII = 432.48 based on OS. Abbreviations: ROC: receiver operating characteristic, SII: systemic immune-inflammation index, OS: overall survival.

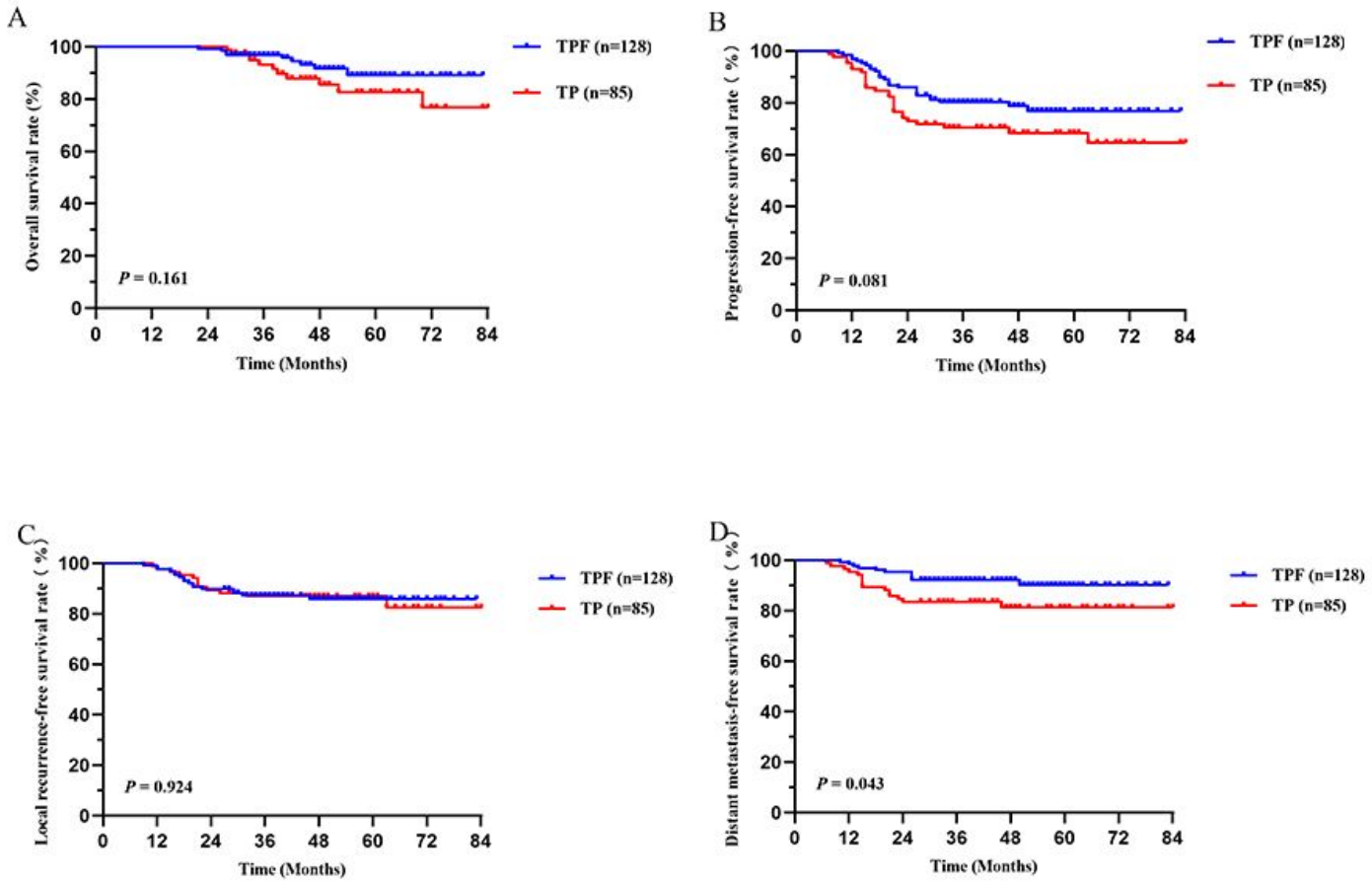

Figure 2

Kaplan-Meier survival curves of OS (A), PFS (B), LRFS (C) and DMFS (D) between TPF and TP groups in locally advanced patients. Abbreviations: TPF: docetaxel, cisplatin, and 5-fluorouracil, TP: docetaxel and cisplatin, OS: overall survival, PFS: progression-free survival, LRFS: locoregional relapse-free survival, DMFS: distant metastasis-free survival.

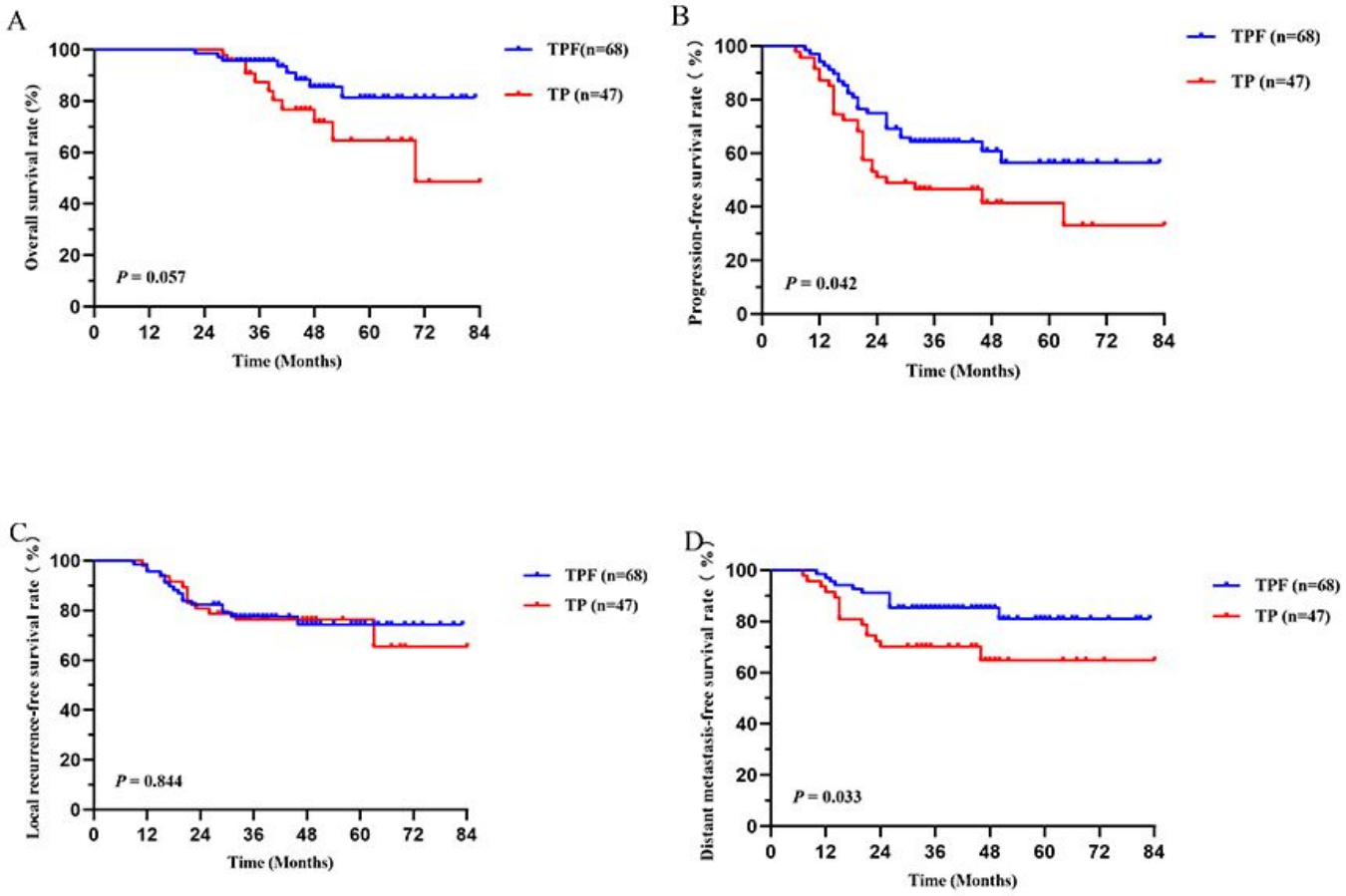

Figure 3

Kaplan-Meier survival curves of OS (A), PFS (B), LRFS (C) and DMFS (D) between TPF and TP groups in patients with stage IVA. Abbreviations: TPF: docetaxel, cisplatin, and 5-fluorouracil, TP: docetaxel and cisplatin, OS: overall survival, PFS: progression-free survival, LRFS: locoregional relapse-free survival, DMFS: distant metastasis-free survival.

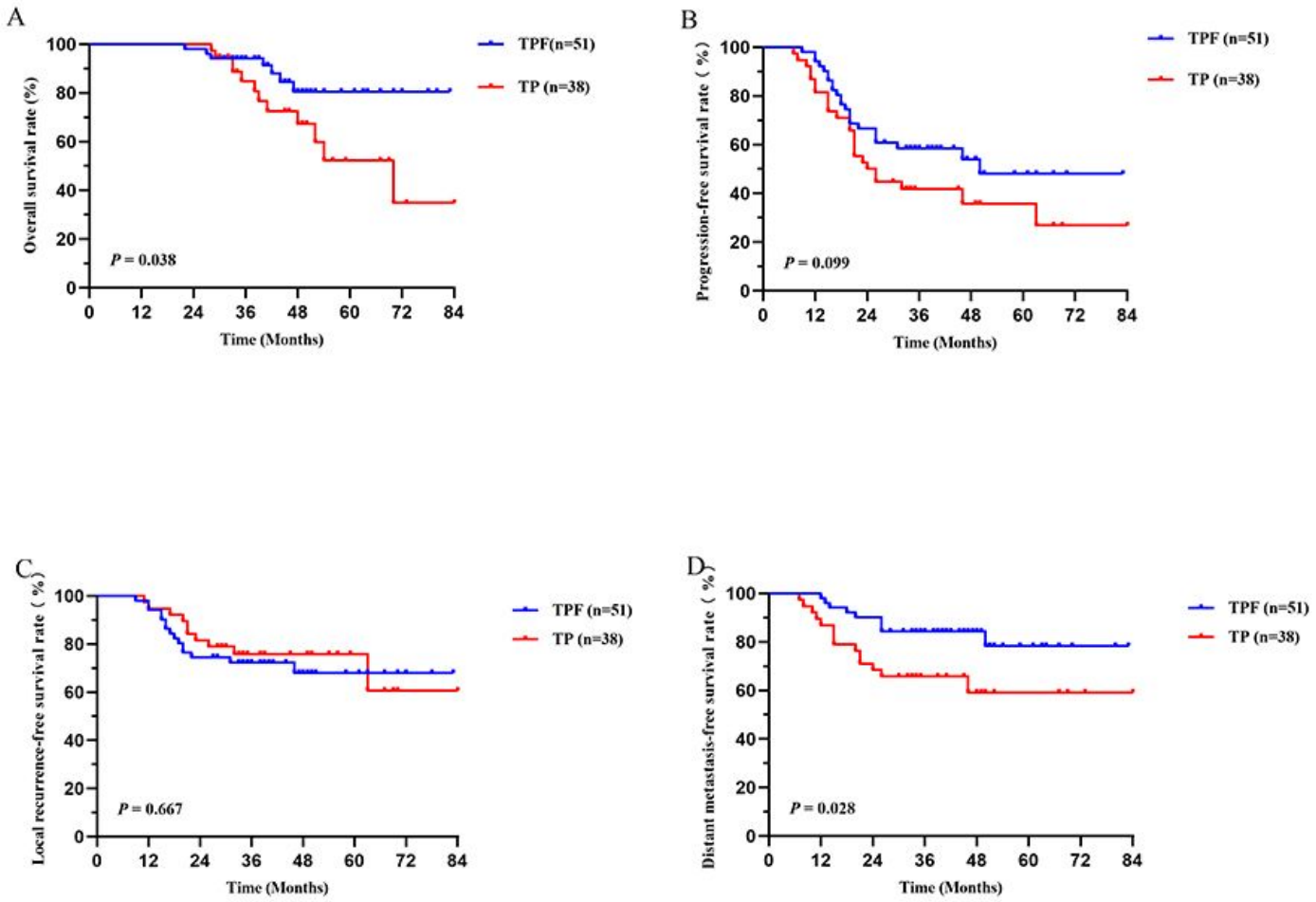

Figure 4

Kaplan-Meier survival curves of OS (A), PFS (B), LRFS (C) and DMFS (D) between TPF and TP groups in stage IVA patients with high SII (SII≥432.48). Abbreviations: TPF: docetaxel, cisplatin, and 5-fluorouracil, TP: docetaxel and cisplatin, OS: overall survival, PFS: progression-free survival, LRFS: locoregional relapse-free survival, DMFS: distant metastasis-free survival.

Supplementary Files

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- SFig31.tif
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