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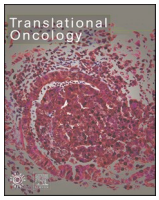

Original Research

Tislelizumab plus neoadjuvant chemotherapy and concurrent chemoradiotherapy versus neoadjuvant chemotherapy and concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma: A retrospective study

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ABSTRACT

Background: The efficacy of immunotherapy plus neoadjuvant chemotherapy and concurrent chemoradiotherapy (CCRT) for locally advanced nasopharyngeal carcinoma (LA-NPC) has not been reported. This study retrospectively compared the efficacy of tislelizumab plus neoadjuvant chemotherapy and CCRT with neoadjuvant chemotherapy followed by CCRT.

Methods: Ninety patients with stages III–IVa NPC were identified between January 2020 and March 2021 at the Affiliate Hospital of Guangdong Medical University. Forty-three patients in the observation group (OG) received tislelizumab plus nano albumin–paclitaxel and cisplatin (nab-TP) regimen, followed by CCRT, while forty-seven patients in the control group (CG) received nab-TP regimen followed by CCRT.

Results: The complete response rate after neoadjuvant therapy was significantly higher in the OG compared to the CG (37.2% vs. 12.8 %). The objective response rates were 88.4 % in the OG and 70.2 % in the CG. The 3-year progression-free survival (PFS) rates for OG and CG patients were 93.0 % and 78.7 %, respectively ($P = 0.04$, HR = 0.31). The overall survival (OS) rates for the OG and the CG were 95.3 % and 87.2 %, respectively ($P = 0.15$, HR = 0.36). Locoregional relapse-free survival (LRFS) rates were 90.7 % for the OG and 72.3 % for the CG ($P = 0.04$, HR = 0.38), and distant metastasis-free survival (DMFS) rates were 95.3 % for the OG, and 80.9 % for the CG ($P = 0.04$, HR = 0.30). For PD-L1 high-expression and low-expression rates, the 3-year PFS rates were 89.2 % and 85.7 % ($P = 0.77$, HR = 1.21), and the OS rates were 90.2 % and 89.2 % ($P = 0.65$, HR = 1.36), respectively.

Conclusion: Tislelizumab combined with neoadjuvant chemotherapy and CCRT showed encouraging therapeutic effects and good tolerability in patients with LA-NPC compared to the standard treatment.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor that originates from the nasopharyngeal epithelial cells. The incidence of NPC varies regionally, with 70 % of new cases occurring in East and Southeast Asia, and China alone accounting for approximately 47.7 % of new cases worldwide [1]. Due to the nasopharynx's concealed location, more than 70 % of patients are diagnosed at a middle or late stage [2]. The 5-year survival rate with radiotherapy alone is only 30–50 % [3]. According to the National Comprehensive Cancer Network 2020 guidelines, sequential neoadjuvant concurrent chemoradiotherapy (sequential CCRT) is the standard of care for locally advanced NPC

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(LA-NPC) [4]. A meta-analysis of multiple neoadjuvant chemotherapies combined with CCRT showed that neoadjuvant chemotherapy improved the overall 5-year survival by 6 % compared to CCRT alone [5]. Moreover, research has suggested that neoadjuvant chemotherapy can reduce the incidence of distant metastasis [6].

Nab-paclitaxel is a complex formed by binding paclitaxel to human albumin proteins, which improves drug efficacy, reduces adverse effects, and offers a convenient mode of administration [7]. A phase II clinical trial investigating the combination of albumin–paclitaxel and cisplatin-induced chemotherapy, along with concurrent radiotherapy and chemotherapy for advanced NPC indicated that after two cycles of neoadjuvant chemotherapy in patients with LA-NPC, the objective response rates (ORRs) were 97.2 % and 100 %, respectively. The most common grade 3–4 acute adverse events during treatment were thrombocytopenia (34.3 %) and leukopenia (28.6 %) [8]. According to the American Society of Clinical Oncology (ASCO) in 2023 [9], a study comparing nano albumin–paclitaxel and cisplatin (nab-TP) versus docetaxel, cisplatin, and fluorouracil (TPF) neoadjuvant chemotherapy followed by concurrent chemoradiation for LA-NPC showed ORRs of 80.28 % in the nab-TP-treated group and 78.26 % in the TPF-treated group after two cycles of neoadjuvant chemotherapy. The most common grade 3 adverse reactions in the nab-TP and the TPF groups, were neutropenia (0.70% vs. 2.16 %), leukopenia (0% vs. 2.88 %), and diarrhea (0% vs. 0.72 %), respectively. No grade 4 adverse reactions were observed in either group. The nab-TP regimen had a similar ORR benefit to the TPF regimen in patients with LA-NPC but a better safety profile. Therefore, the nab-TP regimen is a promising treatment option for neoadjuvant chemotherapy in patients with LA-NPC owing to its significant antitumor effects and mild side effects.

Although neoadjuvant CCRT has improved the survival rate of patients with NPC, approximately 15–25 % of patients still experience treatment failure. Therefore, it is necessary to identify treatment methods that increase efficacy and reduce toxicity based on neoadjuvant sequential CCRT [6,10]. NPC is characterized by abundant lymphocyte infiltration and substantially high expression of programmed cell death ligand 1 (PD-L1). Thus, immune checkpoint inhibitors, particularly programmed cell death receptor-1 (PD-1) inhibitors, have considerable therapeutic potential for NPC. However, three large phase III clinical trials have shown that standard chemotherapy combined with anti-PD-1 monoclonal antibodies (mAbs) improved progression-free survival (PFS) and ORR in patients with recurrent or metastatic NPC. Chemotherapy combined with anti-PD-1 mAbs as a first-line treatment has shown promising results in patients with advanced NPC. The RATIONALE-309 study [11] showed a 14.2 % improvement in ORR and a significant improvement in the complete response rate (CRR) (16% vs. 6.8 %) in the tislelizumab combined with the gemcitabine and cisplatin (GP) group. Tislelizumab combined with neoadjuvant chemotherapy for patients with LA-NPC achieved an ORR of 88.9–95.8 % and a CRR of 11.1–50 % after neoadjuvant therapy [12–14]. Therefore, it has been suggested that tislelizumab shows a good tumor shrinkage effect in both local advanced and advanced NPC.

Tislelizumab (BGB-A317) is an anti-PD-1 monoclonal immunoglobulin (Ig)-G4 antibody with high affinity and specificity for PD-1 and is designed to minimize binding to FcγR on macrophages, thereby eliminating antibody-dependent cell-mediated phagocytosis, a potential resistance mechanism to T-cell clearance and anti-PD-1 therapy [15]. Multiple clinical trials have shown that tislelizumab exhibits potent antitumor activity against various tumors, including NPC [16–18]. Studies on tislelizumab for LA-NPC are ongoing (National Clinical Trial numbers: NCT05342792 and NCT05211232).

Immunotherapy treatment options and strategies for patients with LA-NPC differ. Based on the feasibility of combining immunotherapy with induction chemotherapy (IC) and CCRT for the treatment of NPC, this single-center retrospective study explored the efficacy of tislelizumab combined with neoadjuvant chemotherapy and CCRT versus neoadjuvant chemotherapy and CCRT in patients with LA-NPC. Additionally, the study aimed to explore if neoadjuvant treatment could improve long-term survival benefits.

Materials and methods

Ethics statements

This study was approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical University (PJKT2023–075). All procedures were performed in accordance with the principles of the Declaration of Helsinki.

Study design and participants

We reviewed the medical records of patients with LA-NPC treated with tislelizumab plus nab-TP regimen and CCRT or nab-TP regimen plus CCRT at the Specialty of Head and Neck Oncology of the Affiliated Hospital of Guangdong Medical University (Zhanjiang, Guangdong, China) between January 2020 and March 2021. Inclusion criteria were age 18–70 years, male or non-pregnant female patients, pathologically confirmed nonkeratinizing NPC (ECOG score $\geq$1), measurable lesion (stages III–IVa 8th American Joint Committee on Cancer stage), and absence of previous antitumor therapy. Patients with recurrent distant metastases of NPC pathologically confirmed keratinizing squamous cell carcinoma (classified as type I by the World Health Organization), T3N0 and T3N1 tumors (only retropharyngeal lymph node metastasis) in stages III–IVa, previous radiotherapy or systemic chemotherapy, autoimmune disease or immunosuppression, previous treatment with PD-1/PD-L1 inhibitors or immunosuppressive agents, and other malignant tumors were excluded.

Immunotherapy

Immunotherapy was performed in the observation group (OG). Patients were injected with tislelizumab 200 mg on day 1 of neoadjuvant chemotherapy every 3 weeks for 3 cycles, and tislelizumab 200 mg during CCRT, starting on day 1 of radiotherapy, and every 3 weeks during radiotherapy for 3 cycles.

Chemotherapy

Neoadjuvant chemotherapy was performed in the OG and control group (CG). Patients in the OG (tislelizumab + nab-TP regimen) were injected with tislelizumab 200 mg, nab-paclitaxel 260 mg/m^2, and cisplatin 80 mg/m^2 on day 1, whereas patients in the CG received nab-paclitaxel 260 mg/m^2 and cisplatin 80 mg/m^2 on day 1. Both therapies were repeated every 3 weeks during the three treatment cycles, depending on efficacy. CCRT was administered 3 weeks after the end of neoadjuvant therapy. All patients received a concurrent cisplatin chemotherapy regimen of 100 mg/m^2 every 3 weeks for three cycles during radiotherapy.

Radiotherapy

All the patients underwent intensity-modulated radiation therapy after neoadjuvant chemotherapy (Fig. 1). The prescription dosage was as follows: gross nasopharyngeal tumor target volume (GTVnx), 69.96 Gy; gross tumor lymph node target volume (GTVnd), 69.96 Gy; clinical target volume 1 (CTV1), 60 Gy; and clinical target volume 2 (CTV2), 54 Gy; frequency, once a day, five times a week, a total of 33 times. The normal tissue dose limit and prescription dose requirements were based on QUANTEC's relevant dose-limit standards.

Follow-up

The date of the last follow-up was defined as the last imaging study,

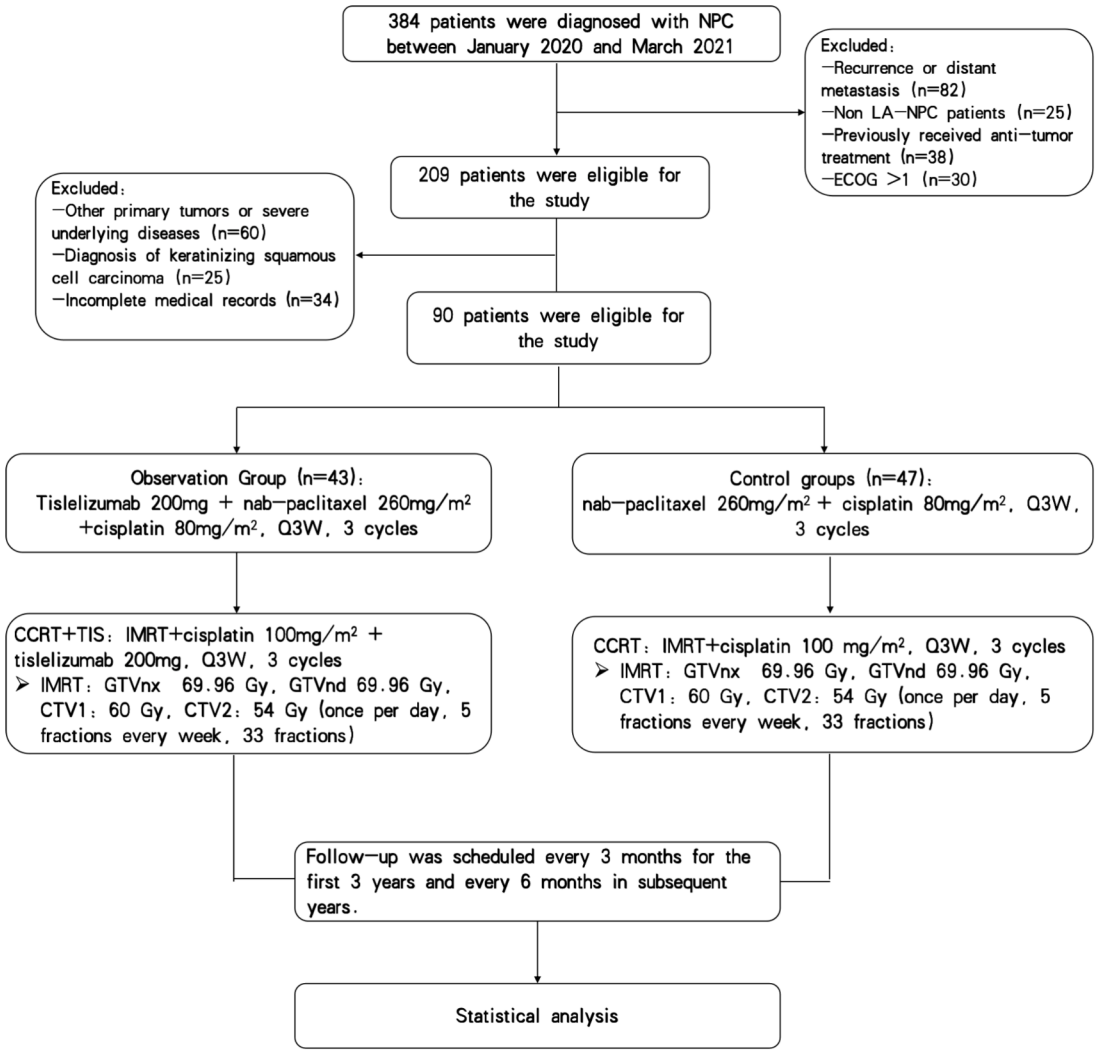

Fig. 1. Study diagram.

clinical visit, and/or telephonic follow-up. The final follow-up data were updated on May 1, 2024. Patients underwent follow-up every 3 months, including physical examinations, nasal endoscopy, magnetic resonance imaging (MRI)/computed tomography of the head and neck, tumor markers, and Epstein–Barr virus DNA. All survival data were calculated from the date of diagnosis to the date of each event or the last follow-up.

Efficacy evaluation

MRI, head and neck imaging (plain + enhanced), and nasal endoscopy were performed every 3 months or whenever disease progression was suspected. Disease assessment was performed according to the Response Evaluation Criteria in Solid Tumors 1.1. The primary endpoint was CRR after neoadjuvant therapy, which was determined by repeat nasopharyngeal and neck MRI at 3 weeks after three cycles of neoadjuvant therapy, with CRR defined as the disappearance of all target lesions on imaging and the shortening of all pathological lymph nodes (whether target or nontarget lesions) to <10 mm in diameter. Secondary endpoints included ORR (defined as the proportion of patients with a certain amount of tumor shrinkage that was maintained for a certain period of time, including cases in complete and partial remission), 3-year PFS (defined as the time to tumor progression or patient death within 3 years), association of PD-L1 expression detection, and correlation of therapeutic efficacy of immune checkpoint inhibitor (ICI) in LA-NPC. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Statistical analysis

Variable distribution was assessed using the Shapiro–Wilk test. Normally distributed variables were compared using the independent samples *t*-test, while non-normally distributed variables were compared using the Wilcoxon rank sum test. Categorical variables, expressed as numbers and percentages, were compared using the chi-square test or Fisher exact test. Survival analyses were performed using the Kaplan–Meier method with 95 % confidence intervals (CIs), and group comparisons were performed using the log-rank test. Statistical analysis was performed using SPSS version 26.0, with statistical significance set at an alpha level of 0.05 ($P < 0.05$).

Results

Patient characteristics

During the study period, 90 patients with LA-NPC were enrolled, including 59 men and 31 women, with a sex ratio of 1.9:1. The median age was 42 years (range: 16–75 years). Among them, 37 patients had stage III cancer and 53 had stage IVa (Fig. 2), with 43 and 47 patients in OG and CG, respectively. All reported parameters were balanced between the two groups with no statistical differences. Detailed baseline

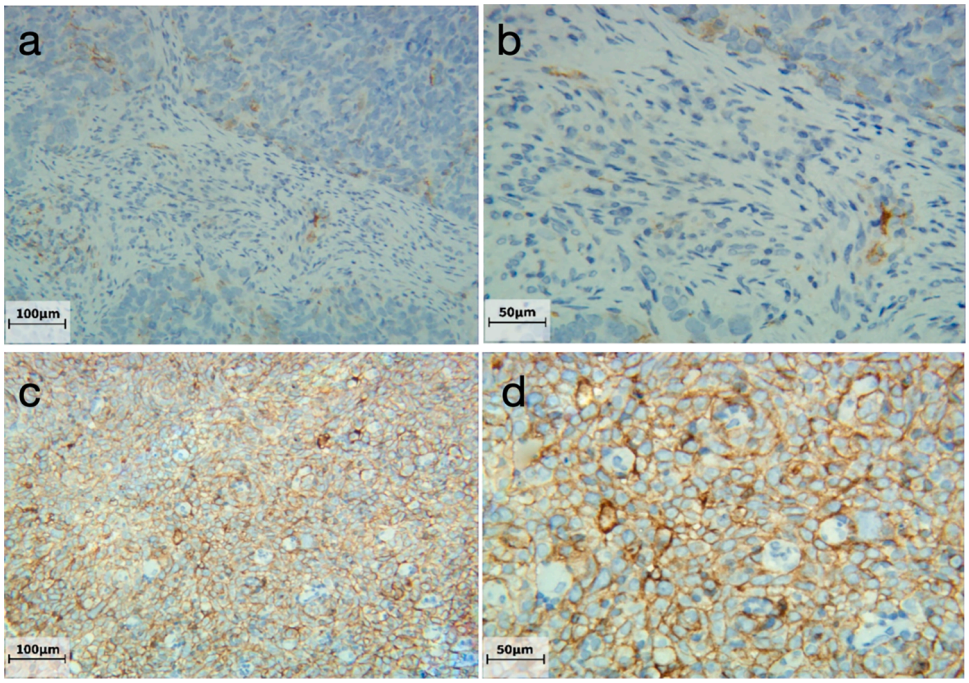

Fig. 2. (a and b) Immunohistochemical staining for PD-L1 expression (SP263) (TC approximately 10 %, IC approximately 1 %). (c and d) Immunohistochemical staining for PD-L1 expression (SP263) (TC approximately 90 %, IC approximately 10 %). PD-L1, programmed cell death ligand 1.

patient characteristics are shown in Table 1.

Survival results

There were 43 patients in OG and 47 patients in CG with a median follow-up of 42 months. The ORRs were 88.4 % in the OG and 70.2 % in the CG. CRRs after neoadjuvant chemotherapy in the entire cohort were 37.2 % and 12.8 %, respectively (Table 2, Figs. 3 and 4). The 3-year PFS rates for patients in the OG and CG were 93.0 % and 78.7 %, respectively ($P = 0.04$, HR = 0.31). OS rates for OG and CG were 95.3 % and 87.2 %, respectively ($P = 0.15$, HR = 0.36), locoregional relapse-free survival (LRFS) rates were 90.7 % for OG and 72.3 % for CG ($P = 0.04$, HR = 0.38), and distant metastasis-free survival (DMFS) rates were 95.3 % for OG and 80.9 % for CG ($P = 0.04$, HR = 0.30). The 3-year PFS for PD-L1 high-expression and low expression rates were 89.2 % and 85.7 %, respectively ($P = 0.77$, HR = 1.21), and the OS rates for PD-L1 high and low expression were 90.2 % and 89.2 %, respectively ($P = 0.65$, HR = 1.36).

Toxicity

The incidences of grades 3 and 4 acute treatment-related adverse events were 70.2 % for the OG and 65.6 % for the CG. The most common grade 3–4 immune-related adverse events were hyperthyroidism (9.3 %), hypothyroidism (7.0 %), and hepatotoxicity (4.7 %). Acute toxic reactions are listed in Table 3 according to the National Cancer Institute General Toxicity Criteria Version 5.0.

Discussion

This retrospective study compared the long-term outcomes among patients with LA-NPC treated with tislelizumab combined with nab-TP neoadjuvant chemotherapy sequential tislelizumab combined with CCRT versus nab-TP neoadjuvant chemotherapy sequential CCRT. We found that after neoadjuvant therapy, the tislelizumab combined with nab-TP group, compared with the CG, showed an increase in CRR of approximately 24.4 % and a 3-year PFS increase of approximately 14.3 %. Additionally, there was no significant difference in adverse effects between the two groups.

An increased CRR may contribute to the long-term survival benefits for patients. A meta-analysis by Tang et al. [19] showed that neoadjuvant chemotherapy significantly improved PFS, OS, DMFS, and LRFS, with controlled toxicity and good survival prognosis compared with CCRT. Current guidelines recommend neoadjuvant chemotherapy, such as TPF, GP, and TP regimens. Zhou et al. [20] reported that compared with CCRT alone, TPF-based IC plus CCRT significantly improved OS and PFS but resulted in an increased risk of hematological toxicities, such as leukopenia and neutropenia, and nonhematological toxicities, such as dysphagia and mucositis, which may lead to decreased patient compliance, thus affecting the efficacy of subsequent radiotherapy. However, preliminary findings by Wang et al. [21] showed that the TP neoadjuvant chemotherapy regimen resulted in a significantly higher survival rate and a lower incidence of neutropenia, anemia, and diarrhea than the TPF regimen and that other adverse effects, including nausea/vomiting and mucositis, did not differ between the two treatment groups. Current Chinese Society of Clinical Oncology (CSCO) guidelines recommend GP regimens as the first-line induction chemotherapy regimens; however, GP regimens exhibit a high hematologic toxicity response [10]. The International Guidelines for Nasopharyngeal Carcinoma 2021, jointly completed by CSCO and ASCO and published in the *Journal of Clinical Oncology*, recommends neoadjuvant chemotherapy with TP regimens [22]. However, paclitaxel requires pretreatment and is prone to adverse effects, such as sodium retention. Nab-paclitaxel, a complex consisting of albumin and paclitaxel, is designed to overcome these drawbacks. The results of a phase II trial of nab-paclitaxel in combination with cisplatin for the treatment of patients with LA-NPC showed encouraging antitumor efficacy and manageable toxicity of nab-paclitaxel in combination with cisplatin as a neoadjuvant chemotherapy regimen [8].

Neoadjuvant chemotherapy combined with CCRT is the standard treatment for LA-NPC; however, there is still 15–25 % recurrence and metastasis. Immune checkpoint blockade therapies, especially PD-1/PD-L1, are novel oncology agents approved by the National Medical Products Administration or Food and Drug Administration. Immunotherapy

Table 1
Baseline patient characteristics.

Characteristics	No. (%)		*P* -value
	OG ($n = 43$)	CG ($n = 47$)	
Gender			0.933
Female	15(34.9)	16(34.0)	
Male	28(65.1)	31(66.0)	
Age			0.456
≥45 years	27(62.8)	33(70.2)	
<45 years	16(37.2)	14(29.8)	
Median	48	53	
Smoking			0.262
Yes	16(37.2)	14(29.8)	
No	27(62.8)	33(70.2)	
Drinking			0.460
Yes	10(23.3)	8(17.0)	
No	33(76.7)	39(83.0)	
BMI (kg/m^2)			0.300
<22	20(46.5)	27(57.4)	
≥22	23(53.5)	20(42.6)	
ECOG score			0.460
0	28(65.1)	34(72.3)	
1	15(34.9)	13(27.7)	
T classification			0.919
T1-T2	16(37.2)	17(36.2)	
T3-T4	27(62.8)	30(63.8)	
N classification			0.218
N0-N1	8(18.6)	14(29.8)	
N2-N3	35(81.4)	33(70.2)	
Solid tumor stage			0.771
III	17(39.5)	20(42.6)	
IVa	26(60.5)	27(57.4)	
EBV DNA (copies/ml)			0.561
≥500	23(53.5)	28(59.6)	
<500	20(46.5)	19(40.4)	
PD-L1 expression on tumor cells(SP263)			0.096
IC0/1 or TC0/1	15(34.9)	20(42.6)	
IC2/3 or TC2/3	25(58.1)	18(38.3)	
Unknown	3(7.0)	9(19.1)	

ECOG, Eastern Cooperative Oncology Group; T, tumor; N, node; M, metastasis; EBV DNA, Epstein–Barr virus deoxyribonucleic acid; PD-L1, programmed cell death ligand 1; TC0 or IC0, <1 % PD-L1-positive TC and/or IC; TC1/2/3 or IC1/2/3, ≥1 % PD-L1-positive TC and/or IC; TC2/3 or IC2/3, ≥5 % PD-L1: positive TC and/or IC.

Table 2
Treatment response.

Treatment response after neoadjuvant chemotherapy	No.(%)		*P* -value
	OG($n =$ 43)	CG($n =$ 47)	
Complete response (CR)	16 (37.2)	6 (12.8)	0.007*
Partial response (PR)	22 (51.2)	27 (57.4)	0.550
Stable disease (SD)	5 (11.6)	13 (27.7)	0.058
Progressive disease (PD)	0 (0)	1 (2.1)	0.336
Objective response (CR + PR)	38 (88.4)	33 (70.2)	0.035*
Disease control rate (CR + PR + SD)	43 (100)	46 (97.9)	0.34

has become a new trend in the treatment of LA-NPC, and various strategies such as neoadjuvant immunotherapy, immunosynchronized chemoradiotherapy, and immunoadjuvant therapy are being explored [15,23,24].

PD-1 monoclonal antibodies combined with chemotherapy provide a theoretical basis for the treatment of LA-NPC. Infiltrating lymphocytes and EBV infection are important factors affecting the immune microenvironment of nasopharyngeal carcinoma tumors, and the expression rate of PD-L1 in EBV antigens is as high as 89–95 %, which provides a possibility for the application of immunotherapeutic drugs in patients with NPC. Recently, an increasing amount of research suggested the clinical value of immunotherapy in the treatment of NPC. However, the long-term survival benefit still has not been reported in LA-NPC. At the annual meeting of the 2023 ASCO, a multicenter phase III clinical study [25] of immune checkpoint inhibitors combined with induction chemotherapy and simultaneous radiotherapy for LA-NPC showed that, with a median follow-up of 42 months, the 3-year event-free survival (EFS) rate of patients treated with PD-1 inhibitors combined with standard treatment increased by 10.1 %, and the risk of events decreased by 41 %. In addition to a 10.1 % improvement in 3-year EFS and a 41 % reduction in the risk of events, the risks of locoregional recurrence and distant metastasis were reduced by 46 % and 43 %, respectively. In terms of safety, there was no significant difference in the incidence of grade 3–4 adverse events between the two groups.

Among PD-1 inhibitors, tislelizumab has shown promising efficacy in clinical trials for various tumors. The multicenter, open, phase I/II study BGB-A317–102 (CTR20160872) reported safety data for 300 patients with solid tumors (including NPC) treated with tislelizumab in China. The entire cohort tolerated the drug well, with no unexpected safety events [16]. Encouragingly, the efficacy of tislelizumab combination therapy has also been demonstrated in several other studies [12,13]. An interim analysis of RATIONALE 309 [11] showed a benefit in the median PFS, ORR, and CRR in the tislelizumab combination GP group compared with the chemotherapy group.

The combination of a PD-1 monoclonal antibody and chemotherapy (nab-TP) can theoretically exert the advantages of high dose, high bioavailability, high efficiency, and low toxicity, as well as eliminate the need for hormonal antiallergic pretreatment. Therefore, we believe that PD-1 monoclonal antibody combined with neoadjuvant chemotherapy has significantly improved efficacy compared with single-agent chemotherapy, with a manageable safety profile and no treatment-related mortality.

Neoadjuvant chemotherapy combined with immunotherapy can shrink primary tumors, provide safer margins for radiotherapy, and reduce organ toxicity. When combined with immunotherapy, chemotherapy can play an immunomodulatory role, exerting a tumor effect by increasing antigenicity, improving immunogenicity, and increasing sensitivity to immune attack. It can also exert an immune system effect by activating intrinsic immunity, activating acquired immunity, and removing immunosuppressive factors. However, several studies have confirmed that neoadjuvant immunotherapy treatment improves long-term survival of lung cancers. Nivolumab plus chemotherapy as a neoadjuvant regimen for resectable lung cancer significantly improved patients' median survival and 1- and 2-year EFS rates. Data from the AEGEAN study [26], presented at the 2023 American Association for Cancer Research Annual Meeting, confirmed that durvalumab as a neoadjuvant+adjuvant therapy for resectable early-stage (stages IIA–IIIB) non-small-cell lung cancer significantly improved the rates of pathologic complete remission (pCR) and 1-year and 2-year EFS. In the KEYNOTE-756 study [27], the addition of pembrolizumab to preoperative neoadjuvant chemotherapy significantly increased pCR rates in patients with early-stage breast cancer. Additionally, we found that immunotherapy in combination with neoadjuvant chemotherapy increased CR rates and prolonged survival. In addition to its direct cytotoxic effect on tumor cells, chemotherapy can increase the immunogenicity of tumor cells, inhibit negative immune signals, and change the immune microenvironment of tumors. These effects exert an immune-enhancing effect that lays a theoretical foundation for the combined application of chemotherapy and immunotherapy. Therefore, the potential of immune combination chemotherapy in neoadjuvant therapy is substantial.

Moreover, PD-1 monoclonal antibodies in combination with radiotherapy have a strong theoretical basis. Ionizing radiation can eradicate tumors, release neoantigens, induce dendritic cell maturation, promote tumor antigen presentation, induce CD8+ *T* cells to infiltrate locally into the tumor, upregulate MHC-I class I molecules, enhance CD8+ *T* cell recognition of tumor antigens, and exert a distant effect. Wang et al. showed that radiotherapy not only promotes the efficacy of immunotherapy but also improves tumor radiosensitization, leading to improved

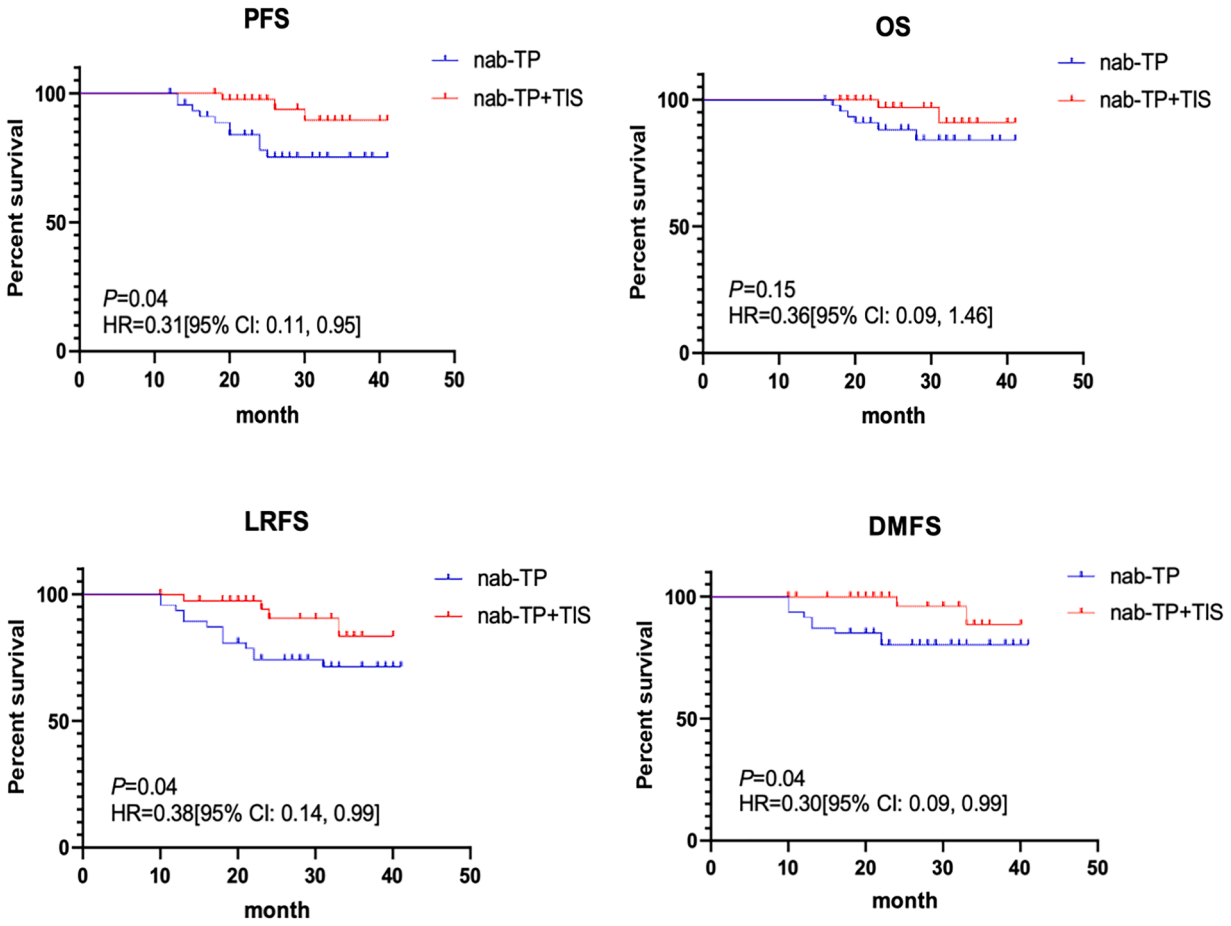

Fig. 3. Kaplan–Meier curves based on the nab-TP regimen or nab-TP+Tis for PFS, OS, LRFS, and DMFS.
nab-TP, nab-cisplatin; nab-TP+Tis, nab-cisplatin+tislelizumab; PFS, progression-free survival; OS, overall survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival.

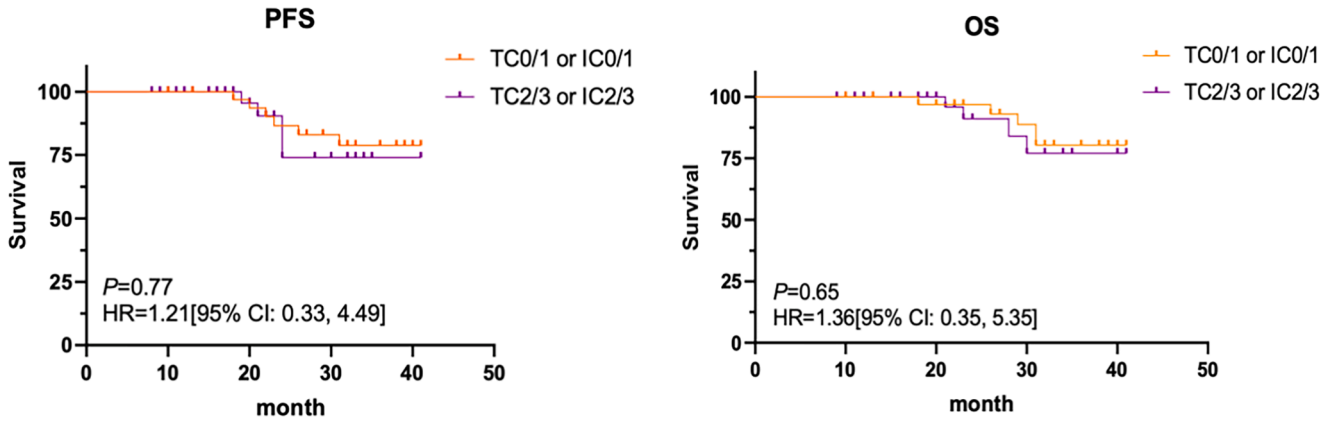

Fig. 4. Kaplan–Meier survival estimates.
TC0 or IC0 (<1 % PD-L1-positive TC and/or IC), TC1/2/3 or IC1/2/3 (≥1 % PD-L1-positive TC and/or IC), and TC2/3 or IC2/3 (≥5 % PD-L1-positive TC and/or IC).

local tumor control. Notably, the distant effect is an interesting phenomenon in radiobiology [28] that leads to the activation of the immune system against cancer cells. Sharabi et al. demonstrated a synergistic effect on local and distant tumor control when radiotherapy was used in combination with immunotherapy. Radiotherapy boosts the use of immunotherapeutic drugs. Currently, large prospective clinical studies of PD-1 monoclonal antibodies in combination with radiotherapy for LA-NPC have not been reported, however, further in-depth exploration is expected in the future. However, the relationship between PFS benefits and biomarkers has been analyzed in these studies, without reaching a uniform conclusion. But the PFS/OS benefits of three different PD-1 monoclonal antibodies were comparable across three phase III studies in recurrent or metastatic nasopharyngeal carcinoma. The RATIONALE-309 study, the only trial to date, suggested that first-line use of tislelizumab in combination with chemotherapy is superior to second-line rescue therapy. The CONTINUUM phase III study reported data on immunotherapy for LA-NPC, showing that the addition of sintilimab to standard IC—CCRT significantly improves EFS.

Table 3
Treatment-related adverse events.

Adverse reactions Number of patients (%)	OG(n = 43)		CG(n = 47)		P Value
	Grade 1–2(%)	Grade 3–4(%)	Grade 1–2(%)	Grade 3–4(%)	
Leukopenia	24(55.8)	7(16.3)	30(63.8)	4(8.5)	0.979
Neutropenia	23(53.5)	4(9.3)	32(68.1)	3(6.4)	0.232
Thrombocytopenia	11(25.6)	5(11.6)	10(21.3)	3(6.4)	0.333
Anaemia	33(76.7)	0 (0)	30(63.8)	0 (0)	0.182
Disgusting	26(60.5)	0 (0)	22(51.2)	0 (0)	0.195
Vomit	19(44.2)	2(4.7)	16(34.0)	1(2.1)	0.224
Trichomadesis	37(86.0)	0 (0)	35(74.5)	0 (0)	0.170
Constipation	25(58.1)	0 (0)	20(42.6)	0 (0)	0.140
Hepatotoxicity	28(65.1)	2(4.7)	20(42.6)	1(2.1)	0.016
Hypothyroidism	7 (16.3)	4(9.3)	1 (2.1)	0 (0)	0.004
Hyperthyroidism	6 (14.0)	3 (7.0)	1 (2.1)	0 (0)	0.016
Rash	13(30.2)	1(2.3)	18(38.3)	2(4.3)	0.329
Diarrhoea	11(25.6)	0 (0)	14(29.8)	0 (0)	0.656
Musculoskeletal pain	2(4.7)	0 (0)	1(2.1)	2(4.3)	0.322
Cough	1(2.3)	0 (0)	1(2.1)	0 (0)	1.000
Fever	2(4.7)	0 (0)	1(2.1)	0 (0)	0.556
Weak	13(30.2)	0 (0)	20(42.6)	1(2.1)	0.505

However, the relationship between specific biomarkers and efficacy was not reported in detail (Table S-1).

The innovation of this study was to explore the use of a PD-1 inhibitor combined with a nab-TP regimen in LA-NPC, which may provide patients with short-term efficacy, long-term survival benefits, and a manageable safety profile. Immunotherapy during CCRT did not lead to any adverse effects. There are three modalities for the timing of anti-PD-1/PD-L1 agents associated with CCRT: induction, concomitant, and consolidation therapies. However, the optimal sequence of immunotherapy and chemoradiation is still under debate, and relevant clinical studies are ongoing (National Clinical Trial numbers: NCT03925090 and NCT04833257 and so on). Considering that patients' outcomes significantly improved in both the neoadjuvant and concurrent radiotherapy phases, we did not consider subsequent immunomaintenance therapy.

This study had several limitations that must be considered. First, this was a single-center study, and the selection of the patient population may not have been comprehensive. Second, this was a retrospective analysis; the results may be affected by residual confounding variables, and the follow-up period may not be long enough to confirm the results of a prospective study.

Conclusions

Compared with regular treatment, the combination of tislelizumab, neoadjuvant chemotherapy, and CCRT showed encouraging therapeutic effects and good tolerability in patients with LA-NPC. A prospective randomized clinical trial is necessary to validate these results.

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Institutional review board statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical University (protocol code: PJKT2023–075; date of approval: 2023–08–03).

Informed consent statement

Not applicable.

CRediT authorship contribution statement

Jiaqi He: Writing – original draft. **Guoqing Luo:** Software. **Shen Liu:** Methodology. **Lingli Chen:** Formal analysis. **Zihong Chen:** Resources. **Bing Zhang:** Data curation. **Jiong Lin:** Software, Conceptualization. **Wenyi Qin:** Writing – original draft. **Haiwen Li:** Writing – original draft. **Haideng Zhou:** Writing – original draft. **Ying Yu:** Validation. **Dechao Zhan:** Validation. **Donghong Yang:** Supervision. **Haiqing Luo:** Project administration.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data is unavailable due to privacy or ethical restrictions.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2024.102058.

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