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# First-Line Immunochemotherapy Versus Palliative Chemotherapy Plus Definitive Radiation Therapy for *de novo* Metastatic Nasopharyngeal Carcinoma: A Matched Cohort Study

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## Abstract

**Background:** The combined use of immune checkpoint inhibitors (ICIs) with palliative chemotherapy (PCT) is a promising first-line treatment for de novo metastatic nasopharyngeal carcinoma (mNPC). However, the efficacy of ICIs with PCT vs PCT with definitive radiation therapy (DRT) remain unclear.

**Methods:** Patients with mNPC who received first-line immunochemotherapy (ICI + PCT) or PCT + DRT were included. Propensity score matching (PSM) was applied to balance potential confounders between patients who did and did not undergo DRT (at a ratio of 1:1). Progression free survival (PFS) and overall survival (OS) were compared between the 2 groups using a log-rank test and Cox proportional hazard model.

**Results:** Among all participants, 149 received ICI + PCT. After PSM, 149 patients were included in the PCT + DRT group. First-line immunochemotherapy was associated with significantly improved PFS (median 9.0 months vs 12.0 months, $P < .001$) and OS (median 12.5 months vs 19.9 months, $P < .001$). Subgroup analysis revealed that tumor response to immunochemotherapy, metastatic organs, and number of metastatic sites potentially affected the efficacy of DRT after first-line immunochemotherapy.

**Conclusion:** Compared with PCT + DRT, first-line immunochemotherapy was associated with improved PFS and OS in patients with mNPC but not in patients with unfavorable tumor response and metastasis involving the liver, distant nodes, or multiple sites.

## Keywords

radiation therapy, nasopharyngeal carcinoma, immune-checkpoint inhibitor

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## Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer that originates in the nasopharynx and is frequently associated with the Epstein–Barr virus (EBV).[1-3] Approximately 10% of diagnosed NPCs are de novo metastatic NPCs (mNPCs), which also have the worst clinical outcomes.

Regarding the treatment of mNPC, the National Comprehensive Cancer Network guideline recommends platinum-based palliative chemotherapy (PCT) as a first-line therapy. However, PCT alone has unfavorable clinical outcomes in the first line treatment of mNPC. Definitive radiation therapy (DRT) is another important treatment modality in mNPC. Combinations of aggressive local treatment with systemic therapy have been associated with increased survival or complete remission in a subset of patients.[4-9] The landmark phase III trial found that the addition of DRT after first-line PCT improved survival in patients with mNPC.[10] However, whether the same efficacy can be achieved through immunotherapy without DRT remains unclear; previous studies showed variable survival rates in patients with mNPC who received DRT after PCT. The prescription of local treatment relies primarily on the patient's response to PCT[3,10,11] and plasma EBV DNA[12] levels, which warrant further investigation in immunochemotherapy settings.

Previous immunotherapeutic strategies in NPC focused on EBV-specific vaccines or T-cell therapy,[13,14] recent studies using immune checkpoint inhibitors (ICIs), primarily targeting the programmed cell death 1 (PD-1) or PD-L1 pathway in the metastatic NPC, have shown promising clinical activity.[15-23] The CAPTAIN-first[16] and JUPITER-02[23] studies compared anti-PD-1 drugs in combination with gemcitabine and cisplatin (GP) chemotherapy vs chemotherapy alone. The results indicated that ICI + PCT was a promising treatment modality for mNPC: The addition of ICI resulted in significantly improved progression-free survival (PFS) and overall survival (OS) with manageable safety profiles.[16,23]

The present study aimed to investigate the efficacy of ICI and PCT combination therapy as the first-line treatment compared to PCT + DRT treatments in patients with mNPC. A subgroup analysis was conducted based on post PCT EBV DNA levels, post immunochemotherapy tumor response, and number of metastatic sites to identify potential factors affecting the efficacy of immunochemotherapy.

## Methods

### Patients

Our study participants were screened from 1211 patients with de novo mNPC being treated at the Sun Yat-Sen University Cancer Center during May 2017 to December 2020, according to the following criteria (Figure 1): (a) aged 18-70 years; (b) stage IV B NPC according to the eighth edition of the American Joint Committee on Cancer staging system; (c) Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade score of 0 or 1; (d) treated with ICI or platinum-based PCT as the first-line treatment; (e) adequate hematological, liver, and renal function parameters. Patients who were pregnant, lactating, or had prior malignancies were excluded from the study. A total of 440 patients with mNPC were included in the study. Finally, propensity score matching (PSM) was used to pair 49 patients in the ICI group with 149 patients in the DRT group. This study was approved by the clinical research and ethics committee of Sun Yat-Sen University Cancer Center (GZKJ-2020-005) and conducted in accordance with the World Medical Association International Code of Medical Ethics (Declaration of Helsinki) for experiments involving humans. Written informed consent was obtained from all participants. We have de-identified patient details such that the identity of any person may not be ascertained in any way.

### Treatment Protocol

All participants received platinum-based PCT for 4 to 6 cycles; 149 patients received ICI followed by maintenance therapy until disease progression or unacceptable toxicity was determined. PCT regimes were administered intravenously every 3 weeks and included docetaxel plus cisplatin (TP, 75 mg/m$^2$ cisplatin with 75 mg/m$^2$ docetaxel on day 1); gemcitabine plus cisplatin (GP, 80 mg/m$^2$ cisplatin with 1 g/m$^2$ gemcitabine on days 1 and 8); cisplatin and fluorouracil (PF, 60-80 mg/m$^2$ cisplatin with 600-800 mg/m$^2$ 5-fluorouracil over 96 h of continuous intravenous infusion); and docetaxel, cisplatin, and fluorouracil (TPF, 60-70 mg/m$^2$ cisplatin, 60-70 mg/m$^2$ docetaxel, and 600-750 mg/m$^2$ 5-fluorouracil over 120 h of continuous intravenous infusion). ICIs were administered intravenously every 3 weeks and included camrelizumab (200 mg on day 1) and toripalimab (240 mg on day 1). After 4 to 6 cycles of PCT, a total of 291 patients received definitive intensity-modulated radiation therapy (IMRT) to the nasopharynx and neck region, as previously described (Supplementary Information).[24] Additionally, 90.6% of irradiated patients received concurrent chemotherapy (cisplatin 80-100 mg/m$^2$) administered intravenously every 3 weeks for 2 to 3 cycles, beginning from the first day of IMRT.

### Data Collection

Before and after PCT, all patients underwent physical and imaging examination, nasopharyngoscopy, and laboratory testing, including complete blood count and biochemical profile analysis.[25] Baseline and post-PCT EBV DNA levels in blood plasma were measured using a quantitative reverse-transcription polymerase chain reaction (qRT-PCR) assay targeting the BamHI-W region of the EBV genome (Sun Yat-Sen University Cancer Center Molecular Diagnostics Department). To evaluate tumor response, CT and/or MRI scans were analyzed post-PCT treatment[26] by 2 independent

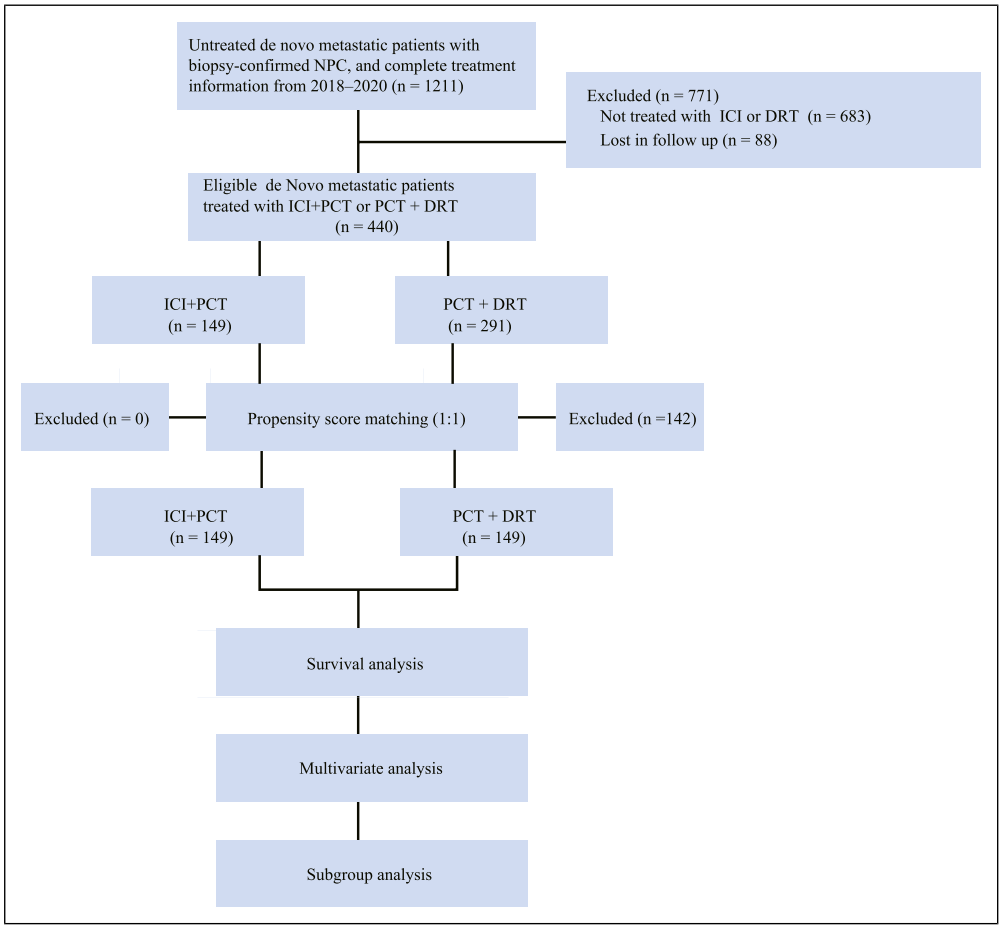


**Figure 1.** Workflow of patient screening. DRT, definitive radiation therapy; ICI, immune checkpoint inhibitors; NPC, nasopharyngeal carcinoma; PCT, palliative chemotherapy.

investigators and classified using the revised response evaluation criteria for solid tumors (version 1.1).[27] Hematologic and non-hematologic toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0.

### *Outcomes and Follow-Up*

The primary endpoint of this study was PFS, calculated from the start of the treatment to the date of first progression, death due to any cause, or patient censoring at the last follow-up. The secondary endpoint was OS, calculated from the start of the treatment to the date of death (due to any cause) or patient censoring at the last follow-up (Supplementary Information).

### *Statistical Analysis*

Statistical analyses were conducted using SPSS version 26.0 (IBM SPSS, Chicago, IL, USA) and R version 4.0.0 (The R foundation, Vienna, Austria). All statistical tests were two-sided, and $P \leq .05$ was considered significant. Propensity scores were calculated using logistic regression with a ratio of 1:1 to balance the covariates of sex, age, ECOG PS, T stage, N stage, metastatic sites, tumor response to chemotherapy, and EBV DNA levels pre- and post-chemotherapy. A $\chi^2$ test and Fisher's exact test were used to compare categorical variables, while the Kaplan-Meier method and log-rank test were used to estimate survival. Multivariate analyses and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model.

## Results

### *Patient Characteristics*

Baseline characteristics were well balanced between the ICI + PCT and PCT + DRT groups (Table 1 and Supplementary Table S1). Patients who received ICI presented more favorable tumor response and lower EBV DNA levels pre- and post-chemotherapy. After a median follow-up period of 23 months (interquartile range: 15-28 months), 273 (62.1%) patients died, and 371 (84.3%) experienced disease progression. In our study, we divided patients with metastatic organs into 5 groups. Groups 1-4: patients with a single metastatic organ

**Table 1.** Baseline characteristics of the study population.

| | The original cohort (%) | | | The matched cohort (%) | | |
|---|---|---|---|---|---|---|
| Characteristic | DRT | ICI | P-value | DRT | ICI | P-value |
| Total | 291 | 149 | | 149 | 149 | |
| Age (in years) | | | | | | |
| <50 | 190 (65.3) | 95 (63.8) | .750 | 91 (61.1) | 95 (63.8) | .632 |
| ≥50 | 101 (34.7) | 54 (36.2) | | 58 (38.9) | 54 (36.2) | |
| Gender | | | | | | |
| Female | 61 (21.0) | 34 (22.8) | .654 | 31 (20.8) | 34 (22.8) | .674 |
| Male | 230 (79.0) | 115 (77.2) | | 118 (79.2) | 115 (77.2) | |
| ECOG | | | | | | |
| 0 | 118 (40.5) | 51 (34.2) | .197 | 64 (43.0) | 51 (34.2) | .122 |
| 1 | 173 (59.5) | 98 (65.8) | | 85 (57.0) | 98 (65.8) | |
| Smoking | | | | | | |
| No | 201 (69.1) | 107 (71.8) | .553 | 100 (67.1) | 107 (71.8) | .379 |
| Yes | 90 (30.9) | 42 (28.2) | | 49 (32.9) | 42 (28.2) | |
| Family history of NPC | | | | | | |
| No | 279 (95.9) | 145 (97.3) | .445 | 141 (94.6) | 145 (97.3) | .239 |
| Yes | 12 (4.1) | 4 (2.7) | | 8 (5.4) | 4 (2.7) | |
| T Stage | | | | | | |
| 1 | 14 (4.8) | 5 (3.4) | .718 | 6 (4.0) | 5 (3.4) | .412 |
| 2 | 37 (12.7) | 15 (10.1) | | 24 (16.1) | 15 (10.1) | |
| 3 | 145 (49.8) | 76 (51.0) | | 66 (44.3) | 76 (51.0) | |
| 4 | 95 (32.6) | 53 (35.6) | | 53 (35.6) | 53 (35.6) | |
| N stage | | | | | | |
| 0 | 2 (.7) | 4 (2.7) | .059 | 2 (1.3) | 4 (2.7) | .136 |
| 1 | 58 (19.9) | 42 (28.4) | | 28 (18.8) | 42 (28.4) | |
| 2 | 90 (30.9) | 41 (27.7) | | 41 (27.5) | 41 (27.7) | |
| 3 | 141 (48.5) | 61 (41.2) | | 78 (52.3) | 61 (41.2) | |
| Pre-treatment EBV DNA | | | | | | |
| Undetectable | 49 (16.8) | 37 (24.8) | .045 | 27 (18.1) | 37 (24.8) | .158 |
| Detectable | 242 (83.2) | 112 (75.2) | | 122 (81.9) | 112 (75.2) | |
| Post-PCT EBV DNA | | | | | | |
| Undetectable | 73 (25.1) | 53 (35.6) | .021 | 39 (26.2) | 53 (35.6) | .079 |
| Detectable | 218 (74.9) | 96 (66.4) | | 110 (73.8) | 96 (66.4) | |
| Post-PCT response | | | | | | |
| CR/PR | 175 (60.1) | 119 (79.9) | < .001 | 121 (81.2) | 119 (79.9) | .770 |
| SD/PD | 116 (39.9) | 30 (20.1) | | 28 (18.8) | 30 (20.1) | |
| Metastatic site | | | | | | |
| Bone metastasis† | 149 (51.2) | 77 (52.7) | .427 | 78 (52.3) | 77 (51.7) | .828 |
| Lung metastasis† | 46 (15.8) | 26 (17.4) | | 25 (16.8) | 26 (17.4) | |
| Liver metastasis† | 29 (10.0) | 10 (6.7) | | 14 (9.4) | 10 (6.7) | |
| Distant node metastasis† | 33 (11.3) | 12 (8.1) | | 8 (5.4) | 12 (8.1) | |
| Multiple metastatic sites‡ | 34 (11.7) | 24 (16.1) | | 24 (16.1) | 24 (16.1) | |

DRT, definitive radiation therapy; EBV, Epstein–Barr virus; ECOG, Eastern Cooperative Oncology Group; ICI, immune-checkpoint-inhibitor; N stage, node stage; NPC, nasopharyngeal carcinoma; PCT, palliative chemotherapy; T stage, tumor stage.

†Patients with a single metastatic organ and ≤3 metastatic sites.

‡Patients with multiple metastatic organs or >3 metastatic sites. P-values were calculated using the Pearson $\chi^2$ test.

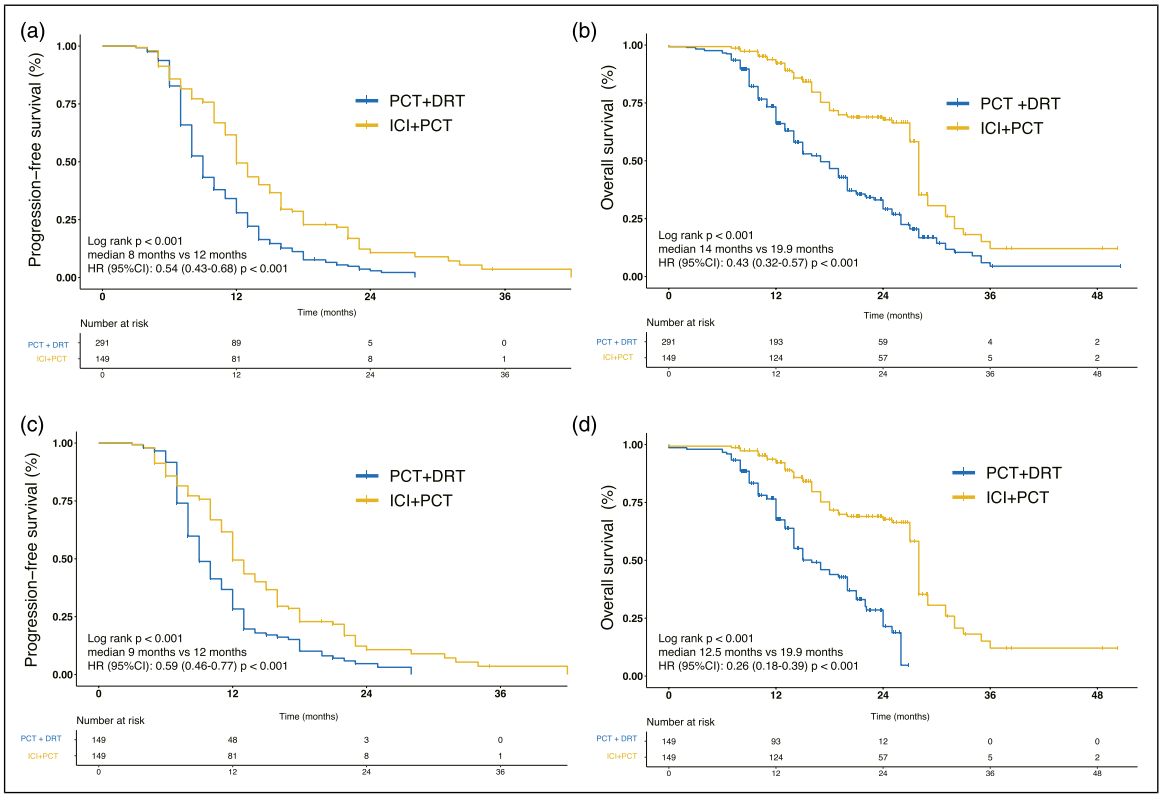


**Figure 2.** Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) for patients with de novo mNPC receiving ICI or DRT as the first-line treatment in (**A, B**) the original and (**C, D**) matched cohort. DRT, definitive radiation therapy; ICI, immune-checkpoint-inhibitor; HR, hazard ratio; PCT, palliative chemotherapy.

and ≤3 metastatic sites; group 5: patients with multiple metastatic organs or >3 metastatic sites.[28]

## Survival Rates

For patients in the original cohort receiving first-line ICI + PCT and PCT + DRT, the median PFS was 12.0 (95% CI: 11.0-13.2) and 8.0 (95% CI: 7.0-9.0) months, respectively, while the median OS was 19.9 (95% CI: 17.0-22.8) and 14.0 (95% CI: 13.0-15.0) months, respectively (Figure 2A–B). Following PSM, the median PFS and OS of patients in the matched DRT group were 9.0 (95% CI: 8.4-9.8) and 12.5 (95% CI: 12.0-13.8) months, respectively (Figure 2C–D). ICI was associated with significantly improved PFS (HR: .59, 95% CI: .46-.77, P < .001) and OS (HR: .26, 95% CI: .18-.39, P < .001) in patients with mNPC.

Excluding ICI, univariate Cox analyses revealed that the detectable EBV DNA level post-immunochemotherapy (HR: 2.53, 95% CI: 1.85-3.46, P = .001), suboptimal tumor response to immunochemotherapy (HR: 2.18, 95% CI: 1.62-2.95, P = .001), liver metastasis (HR: 4.27, 95% CI: 3.59-9.23, P = .001), and multiple metastasis (HR: 2.43, 95% CI: 1.69-3.49, P = .001) were risk factors of PFS (Table 2). In a multivariate analysis, ICI was determined to be an independent prognostic factor of PFS (HR: .63, 95% CI: .48-.82, P = .001).

In terms of OS, univariate analyses revealed that the detectable EBV DNA level post-immunochemotherapy (HR: 1.83, 95% CI: 1.25-2.67, P = .002), suboptimal tumor response to immunochemotherapy (HR: 1.79, 95% CI: 1.20-2.66, P = .002), liver metastasis (HR: 2.41, 95% CI: 1.44-4.01, P = .001), and multiple metastasis (HR: 1.744, 95% CI: 1.13-2.67, P = .001) were associated with adverse outcomes. According to the multivariate analysis, ICI was an independent prognostic factor of OS (HR: .25, 95% CI: .17-.37, P = .001).

## Subgroup Analysis

We performed subgroup analyses to identify potential factors affecting the efficacy of first-line immunochemotherapy in patients with mNPC. EBV DNA level post-immunochemotherapy did not impact the efficacy of ICI: patients with both undetectable and detectable EBV DNA had improved PFS and OS after treatment (Figure 3, Supplementary Table S2). In contrast, tumor response to immunochemotherapy significantly affected treatment efficacy. Patients who presented an optimal response (partial response or complete response) after immunochemotherapy could benefit from ICI (HR for PFS: .55, 95% CI: .41-.74, P < .001; HR for OS: .23, 95% CI: .15-.37, P < .001) instead of

**Table 2.** Cox analysis of progression-free survival (PFS) and overall survival (OS) in the matched cohort.

| | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | Univariate HR (95% CI) | P-value | Multivariate HR (95% CI) | P-value | Univariate HR (95% CI) | P-value | Multivariate HR (95% CI) | P-value |
| Age | | | | | | | | |
| <50 | Reference | | — | — | Reference | | — | — |
| ≥50 | 1.01 (.89-1.15) | .871 | — | — | .89 (.60-1.31) | .547 | — | — |
| Gender | | | | | | | | |
| Female | Reference | | — | — | Reference | | — | — |
| Male | 1.11 (.81-1.51) | .512 | — | — | .76 (.54-1.05) | .101 | — | — |
| Smoking | | | | | | | | |
| No | Reference | | — | — | Reference | | — | — |
| Yes | .98 (.86-1.13) | .825 | — | — | 1.22 (.88-1.70) | .231 | — | — |
| NPC family history | | | | | | | | |
| No | Reference | | — | — | Reference | | — | — |
| Yes | 1.13 (.75-1.70) | .548 | — | — | .64 (.24-1.73) | .378 | — | — |
| ECOG | | | | | | | | |
| 0 | Reference | | — | — | Reference | | — | — |
| 1 | .89 (.68-1.15) | .360 | — | — | .815 (.59-1.12) | .206 | — | — |
| Post PCT EBV DNA | | | | | | | | |
| 0 | Reference | | Reference | | Reference | | Reference | |
| >0 | 2.53 (1.85-3.46) | .001 | 2.00 (1.45-2.76) | .000 | 1.83 (1.25-2.67) | .002 | 1.37 (.92-2.04) | .123 |
| Tumor response | | | | | | | | |
| PR/CR | Reference | | Reference | | Reference | | Reference | |
| PD/SD | 2.18 (1.62-2.95) | .001 | 1.92 (1.40-2.62) | .000 | 1.79 (1.20-2.66) | .004 | 2.02 (1.30-3.13) | .002 |
| Treatment | | | | | | | | |
| PCT + DRT | Reference | | Reference | | Reference | | Reference | |
| ICI + PCT | .59 (.46-.77) | .001 | .63 (.48-.82) | .001 | .27 (.18-.39) | .001 | .25 (.17-.37) | .001 |
| TSstage | | | | | | | | |
| 1 | Reference | | — | — | Reference | | — | — |
| 2 | 1.43 (.66-3.12) | .364 | — | — | 1.43 (.54-3.83) | .471 | — | — |
| 3 | 1.38 (.68-2.83) | .376 | — | — | 1.27 (.51-3.15) | .604 | — | — |
| 4 | 1.37 (.66-2.85) | .394 | — | — | 1.19 (.48-2.99) | .709 | — | — |
| N stage | | | | | | | | |
| 0 | Reference | | — | — | Reference | | — | — |
| 1 | 1.60 (.58-4.45) | .364 | — | — | 1.21 (.29-5.07) | .791 | — | — |
| 2 | 2.02 (.73-5.60) | .175 | — | — | 1.39 (.34-5.75) | .647 | — | — |
| 3 | 1.81 (.66-4.92) | .248 | — | — | 1.36 (.33-5.35) | .668 | — | — |
| Metastatic organs | | | | | | | | |
| Bone† | Reference | | Reference | | Reference | | Reference | |
| Lungs† | .84 (.57-1.24) | .377 | .92 (.62-1.38) | .704 | .84 (.52-1.35) | .471 | .84 (.52-1.37) | .502 |
| Livers† | 4.27 (3.59-9.23) | .001 | 4.17 (2.56-6.79) | .001 | 2.41 (1.44-4.01) | .001 | 1.66 (.97-2.82) | .063 |
| Distant nodes† | 1.02 (.59-1.75) | .945 | 1.14 (.66-1.99) | .621 | 1.23 (.66-2.28) | .501 | 1.35 (.72-2.51) | .346 |
| Multiple sites‡ | 2.43 (1.69-3.49) | .001 | 2.59 (1.78-3.75) | .001 | 1.74 (1.13-2.67) | .001 | 1.59 (1.03-2.45) | .034 |
| Alkaline phosphatase (U/L) | | | | | | | | |
| ≤50 | Reference | | Reference | | Reference | | Reference | |
| >50 | 1.43 (1.01-2.05) | .044 | 1.31 (1.92-1.89) | .138 | 1.79 (1.20-2.67) | .004 | 1.56 (.96-2.21) | .076 |
| C-reactive protein (g/mL) | | | | | | | | |
| ≤3 | Reference | | — | — | Reference | | Reference | — |
| >3 | .82 (.58-1.17) | .289 | — | — | .57 (.38-.86) | .007 | .93 (.48-1.81) | — |
| Lactate dehydrogenase (U/L) | | | | | | | | |
| ≤245 | Reference | | — | — | Reference | | — | — |
| >245 | 1.21 (.78-1.89) | .386 | — | — | 1.19 (.74-1.93) | .468 | — | — |

CI, confidence interval; DRT, definitive radiation therapy; EBV, Epstein–Barr virus; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; NPC, nasopharyngeal carcinoma; PCT, palliative chemotherapy.

†Patients with a single metastatic organ and ≤3 metastatic sites.

‡Patients with multiple metastatic organs or >3 metastatic sites.

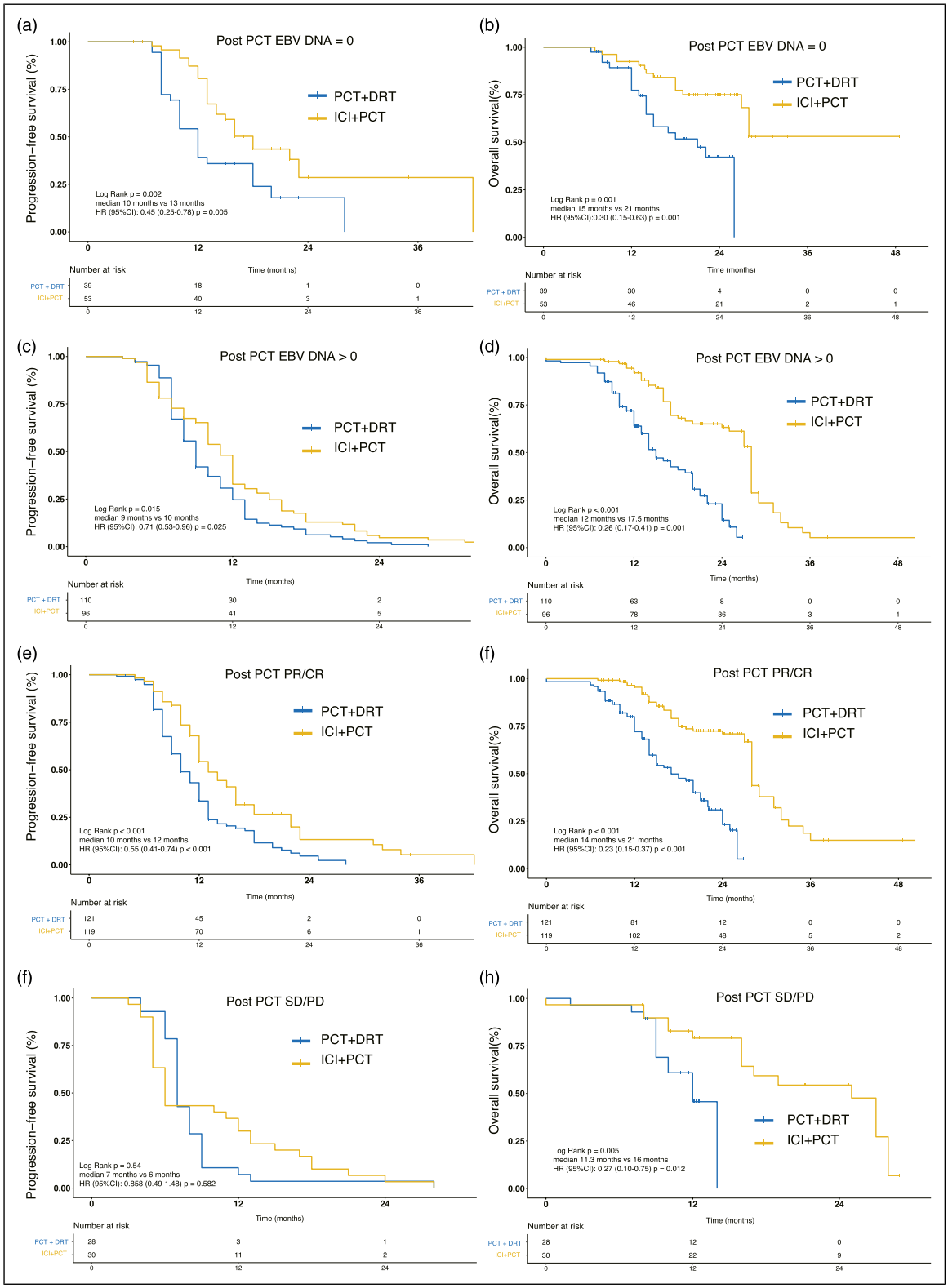


**Figure 3.** Kaplan-Meier curves of PFS and OS for patients with different post treatment Epstein–Barr virus (EBV) DNA levels and tumor response statuses stratified by ICI or DRT in the matched cohort. DRT, definitive radiation therapy; HR, hazard ration; ICI, immune checkpoint inhibitor; PCT, palliative chemotherapy.

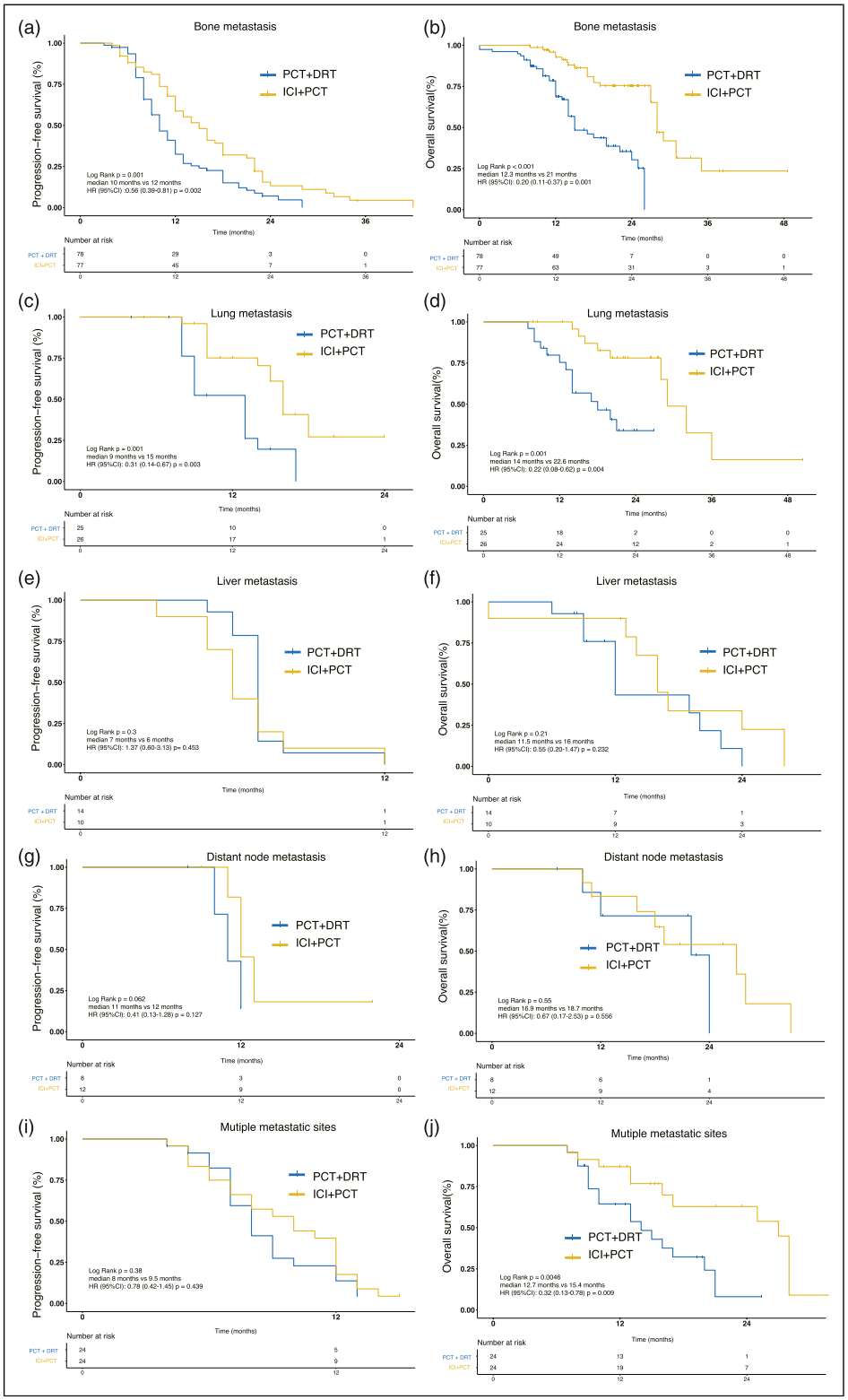


**Figure 4.** Kaplan-Meier curves of PFS and OS for patients with different metastatic sites stratified by ICI or DRT in the matched cohort. DRT, definitive radiation therapy; ICI, immune checkpoint inhibitor; PCT, palliative chemotherapy.

DRT. For patients who presented a suboptimal response (stable disease or progression) after immunochemotherapy, ICI failed to improve PFS (HR: .86, 95% CI: .49-1.48, P = .582) but was associated with better OS (HR: .27, 95% CI: .10-.75, P = .012).

In terms of the disease burden of metastasis, subgroup analyses revealed that metastatic organs and number of metastatic sites were associated with the variable treatment efficacy of ICI (Figure 4, Supplementary Table S2). ICI improved survival in patients with bone and lung metastasis. With liver metastasis, no significant differences were observed in PFS (HR: .41, 95% CI: .13-1.28, P = .127) or OS (HR: .67, 95% CI: .17-2.53, P = .556) for patients receiving ICI + PCT or PCT + DRT. In patients with multiple metastasis involving ≥2 organs or ≥3 sites, ICI did not improve PFS (HR: .78, 95% CI: .42-1.45, P = .439) but was related to better OS (HR: .32, 95% CI: .13-.78, P = .009).

### *Toxicity*

Treatment-related toxicity was recorded for all participants and included acute toxicity as well as radiation-induced complications for patients in the DRT group (Supplementary Table S3). DRT was associated with higher frequencies of grade 3-4 leucopoenia, neutropenia, and anemia.

## Discussion

The combined use of PCT and ICI has been widely applied in clinical practice and is becoming the standard first-line treatment for mNPC.[16,23] However, it remains unclear whether ICI could effectively replace DRT as an additional treatment. This is the first study to evaluate the differences in the response of patients with mNPC to ICI and DRT. We found that PCT + ICI improved PFS and OS in patients with mNPC compared with PCT + DRT.

In our cohort, camrelizumab and toripalimab were the most commonly used ICIs with a median of 20 cycles. GP was the most commonly used PCT regimen with 68-70% of the patients receiving PCT for at least 5 cycles. In both the original and matched cohorts, ICI + PCT was recommended as first-line immunochemotherapy above PCT + DRT. Better survival outcomes (PFS and OS) were observed in patients treated with PCT + ICI and the overall adverse effects of DRT after first-line treatment are higher.

Detectable EBV DNA level post-chemotherapy, suboptimal tumor response to chemotherapy, metastatic organ, and multiple metastasis were identified as risk factors in PFS and OS. In multivariate analyses including the above factors as well as ICI, ICI was identified as an independent risk factor in PFS and OS. In our subgroup analysis, ICI showed better survival outcomes (PFS and OS), regardless of post chemotherapy EBV DNA levels. Moreover, patients with favorable post chemotherapy responses were more suitable for PCT + ICI than DRT, in contrast to previously reported results.[29] For patients with lung and bone metastasis, ICI showed better survival outcomes; however, ICI did not improve survival in patients with liver and distant node metastasis. In patients with multiple metastatic sites, ICI may increase 2-year OS rates (P = .0046) but not in PFS. This may be due to the abscopal effect of local radiotherapy and the combined effect of radiotherapy and immunotherapy.[30,31] However, because our cohort only included 58 patients with multiple metastatic sites, this finding needs to be verified with a larger cohort.

Although we found that PCT + ICI is a better way to treat mNPC compared with PCT + DRT, other therapy strategies such as PCT + ICI + DRT was not included in this study. According to our cohort and previous study,[16,23] ICI do not bring significant side effects to the patients in PCT + ICI group, and is safe for mNPC patients. That is, we can assume that ICI + DRT or PCT + ICI + DRT may be safe and bring more survival benefits compared with PCT + ICI. Therefore, the above new ICI treatment patterns should be further studied in the future.

We acknowledge some limitations to our study design. First, this was a retrospective study conducted at a single cancer center, due to which selection bias was unavoidable and the sample size was not calculated. Second, the ICI used in this study was procured mainly from 2 manufacturers and thus the results were mostly applicable for patients receiving camrelizumab and toripalimab. Third, this study was lack of analysis of genotoxicity of treatment, especially ICI treatment. Fourth, we did not acquire biopsy or blood sample for sequencing analysis or performed immunohistochemistry study. Fifth, we could not acquire the life quality data though the quality-of-life scale. Nevertheless, this study provides a reliable empirical basis for future prospective randomized multicenter studies.

## Conclusions

This is the largest clinical analysis to compare the efficacy of ICI and DRT in the first-line treatment of patients with mNPC. Compared to DRT, first-line immunochemotherapy improved PFS and OS with manageable safety profiles. The treatment efficacy of ICI may be limited in patient subgroups with unfavorable post-immunochemotherapy tumor response and metastasis involving liver, distant nodes, and multiple sites.

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### Declaration of Conflicting Interests

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## Ethical Approval

This study was approved by the clinical research and ethics committee of Sun Yat-Sen University Cancer Center (GZKJ-2020-005) and conducted in accordance with the World Medical Association International Code of Medical Ethics (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained from all patients.

## Data Availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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## Supplemental Material

Supplement material for this article is available in online.

## References

1. Zhang Y, Chen L, Hu G, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N Engl J Med*. 2019;381(12):1124-1135.
2. Zhang LL, Huang MY, Fei X, et al. Risk stratification for nasopharyngeal carcinoma: a real-world study based on locoregional extension patterns and Epstein-Barr virus DNA load. *Ther Adv Med Oncol*. 2020;12:1758835920932052.
3. Chen Y-P, Chan ATC, Le Q-T, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *Lancet*. 2019;394(10192):64-80.
4. Zhong L, Wu D, Peng W, et al. Safety of PD-1/PD-L1 inhibitors combined with palliative radiotherapy and anti-angiogenic therapy in advanced hepatocellular carcinoma. *Front Oncol*. 2021;11:686621.
5. Wu S, Yuan C, Chen L, et al. Survival benefits of anti-PD-1 therapy in combination with radiotherapy in chinese melanoma patients with brain metastasis. *Front Oncol*. 2021;11:646328.
6. Samuel E, Lie G, Balasubramanian A, et al. Impact of radiotherapy on the efficacy and toxicity of anti-PD-1 inhibitors in metastatic NSCLC. *Clin Lung Cancer*. 2021;22(3):e425-e430.
7. McCarthy PM, Rendo MJ, Uy MD, et al. Near complete pathologic response to PD-1 inhibitor and radiotherapy in a patient with locally advanced pancreatic ductal adenocarcinoma. *OncoTargets Ther*. 2021;14:3537-3544.
8. Koukourakis IM, Giakzidis AG, Kouroupi M, et al. Cutaneous squamous-cell carcinoma of the head-neck area refractory to chemo-radiotherapy: Benefit from anti-PD-1 immunotherapy. *BJR Case Rep*. 2021;7(3):20200170.
9. Sato H, Okonogi N, Nakano T. Rationale of combination of anti-PD-1/PD-L1 antibody therapy and radiotherapy for cancer treatment. *Int J Clin Oncol*. 2020;25(5):801-809.
10. You R, Liu YP, Huang PY, et al. Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in de novo metastatic nasopharyngeal carcinoma: A multicenter Phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6(9):1345-1352.
11. Bensouda Y, Kaikani W, Ahbeddou N, et al. Treatment for metastatic nasopharyngeal carcinoma. *European Annals of Otorhinolaryngology, Head and Neck Diseases*. 2011;128(2):79-85.
12. Li WZ, Lv SH, Liu GY, et al. Development of a prognostic model to identify the suitable definitive radiation therapy candidates in de novo metastatic nasopharyngeal carcinoma: A real-world study. *Int J Radiat Oncol Biol Phys*. 2021;109(1):120-130.
13. Le QT, Colevas AD, O'Sullivan B, et al. Current treatment landscape of nasopharyngeal carcinoma and potential trials evaluating the value of immunotherapy. *J Natl Cancer Inst*. 2019;111(7):655-663.
14. Thakur A, Parra DC, Motallebnejad P, Brocchi M, Chen HJ. Exosomes: Small vesicles with big roles in cancer, vaccine development, and therapeutics. *Bioact Mater*. 2022;10:281-294.
15. Hsu C, Lee SH, Ejadi S, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: Results of the KEYNOTE-028 study. *J Clin Oncol*. 2017;35(36):4050-4056.
16. Yang Y, Qu S, Li J, et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): A multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2021.
17. Fang W, Yang Y, Ma Y, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: Results from two single-arm, phase 1 trials. *Lancet Oncol*. 2018;19(10):1338-1350.
18. Kwong DLW. Camrelizumab for nasopharyngeal carcinoma: A new hope? *Lancet Oncol*. 2018;19(10):1266-1267.
19. Wang FH, Wei XL, Feng J, et al. Efficacy, safety, and correlative biomarkers of toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: A phase II clinical trial (POLARIS-02). *J Clin Oncol*. 2021;39(7):704-712.
20. Hoy SM. Sintilimab: First Global Approval. *Drugs*. 2019;79(3):341-346.

21. Desai J, Deva S, Lee JS, et al. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. *J Immunother Cancer*. 2020;8(1).
22. Lv JW, Li JY, Luo LN, Wang ZX, Chen YP. Comparative safety and efficacy of anti-PD-1 monotherapy, chemotherapy alone, and their combination therapy in advanced nasopharyngeal carcinoma: findings from recent advances in landmark trials. *J Immunother Cancer*. 2019;7(1):159.
23. Xu R-h, Mai H-Q, Chen Q-Y, et al. JUPITER-02: Randomized, double-blind, phase III study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). *J Clin Oncol*. 2021;39(18_suppl):LBA2-LBA2.
24. Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol*. 2015;16(6): 645-655.
25. Tian YM, Zeng L, Wang FH, et al. Prognostic factors in nasopharyngeal carcinoma with synchronous liver metastasis: A retrospective study for the management of treatment. *Radiat Oncol*. 2013;8:272.
26. Lee A, Chow JCH, Lee NY. Treatment deescalation strategies for nasopharyngeal cancer: A review. *JAMA Oncol*. 2021;7(3):445-453.
27. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
28. Sun XS, Liu SL, Liang YJ, et al. The role of capecitabine as maintenance therapy in de novo metastatic nasopharyngeal carcinoma: A propensity score matching study. *Cancer Commun*. 2020;40(1):32-42.
29. Sun XS, Liu LT, Liu SL, et al. Identifying optimal candidates for local treatment of the primary tumor among patients with de novo metastatic nasopharyngeal carcinoma: A retrospective cohort study based on Epstein-Barr virus DNA level and tumor response to palliative chemotherapy. *BMC Cancer*. 2019;19(1):92.
30. Reynders K, Illidge T, Siva S, Chang JY, De Ruysscher D. The abscopal effect of local radiotherapy: Using immunotherapy to make a rare event clinically relevant. *Cancer Treat Rev*. 2015; 41(6):503-510.
31. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. *Nat Rev Cancer*. 2018;18(5):313-322.